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THE ROLE OF A B O INCOMPATIBILITY AS A CAUSE OF ERYTHROBLASTOSIS FŒTALIS, WITH REPORT OF A CASE.

By LUCY M. BRYCE, RACHEL JAKOBOWICZ and ELIZABETH K. TURNER.

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THE discovery of the Rh factor soon led to the realization that Rh incompatibility between mother and fœtus could result in maternal immunization expressing itself in the development of Rh antibodies and consequently in the damage of fœtal tissues by these antibodies. This observation has focused the attention of clinicians and laboratory workers once again on the possible effect of any blood group discrepancy between mother and child. A B O incompatibility is particularly interesting, as in such heterospecific pregnancies there are already present in the maternal blood physiological genetically determined antibodies reactive against the child's antigens. In the A B O system fœtal stimulation therefore can either increase these, or alternatively produce an antibody of perhaps different structure but with the same specificity.

A large number of papers have been published showing the frequent serological effect of heterospecific pregnancy—a rise in the corresponding maternal iso-agglutinin—and in contrast, the occasional clinical effect—a child damaged by the action of this rising maternal antibody titre.

In most reported cases of hæmolytic disease of the newborn due to A B O incompatibility, the serological evidence is mainly based on the rise of the corresponding maternal iso-agglutinin titre after the presence of any other blood group antibody has been excluded. In order to show that the antibody present is of immune type, different techniques have been adopted, such as comparison of titres and character of agglutination of albumin and saline suspensions (Boorman and Dodd, 1947), of results obtained with washed and unwashed cells (Gurevitch *et alii*, 1949), or of differences in thermal amplitude (Hubinont, 1949). A titre higher at 37° than at 4° C. is assumed to indicate that the antibody is of immune type, the reaction being reversed with the naturally occurring type. The method which we have used is the absorption of the saline agglutinins with A and B substance as suggested by Witebsky (1948), followed by demonstration and titration of the incomplete type by (i) the indirect Coombs method, (ii) the plasma albumin method, and (iii) the use of trypsinated cells. We have not succeeded in demonstrating these incomplete antibodies by the blocking method described by Wiener for the Rh system (1944).

This paper deals with three consecutive heterospecific pregnancies in the same woman, who belonged to blood group O, while the children were of blood group A. Unfortunately, the data concerning the first two pregnancies are not complete, as many of the laboratory methods necessary for a full investigation are fairly recent ones.

Report of a Case.

The patient, Mrs. W.P., is of blood group O, Rh_1rh, N, Le^a-negative, P-positive. Her first pregnancy in 1944 had resulted in a living male of blood group A, born at seven months' gestation. This baby rapidly developed very severe jaundice and died twenty-eight hours after birth. The post-mortem findings were *erythroblastosis fœtalis*, kernicterus, open *foramen ovale* and patent *ductus arteriosus*.

TABLE I.

Serological Data Concerning Mrs. W.P.'s First and Second Pregnancies.

Blood Group.	Pregnancy.	Time of Test.	Mother. Iso-Agglutinin Titre. Anti-A.	Mother. Iso-Agglutinin Titre. Anti-B.	Mother. Iso-Hæmolysin Titre. Anti-A.	Mother. Iso-Hæmolysin Titre. Anti-B.	Children.
O, R_1r N Le^a-negative P-positive.	First.	8 weeks' gestation.	512	32	64	4	Group A, Rh-positive (Rh tests with anti-Rh_0 serum only).
		2 days after delivery.	16,000	128			
	Second.	8 weeks' gestation.	2,000	32			Group A, Rh-positive (R_1r); "Coombs-negative"; secretor.
		12 weeks' gestation.	1,000	32			
		34 weeks' gestation.	500	32			
		Delivery.	500	32			
		6 days after delivery.	2,000	64			

In April, 1948, she was delivered three weeks prematurely of her second child, a living male. His blood group was A and he was a secretor. The Coombs test on the cord blood produced a negative result. This infant developed mild icterus, but did not require a blood transfusion. However, he had a congenital heart lesion and is now subject to anginal attacks.

Serological investigations showed that when Mrs. W.P.'s first pregnancy was of eight weeks' duration her agglutinin titres were: anti-A, 512; anti-B, 32. Two days after delivery of a group A child they had risen to the following figures: anti-A, 16,000; anti-B, 128. Her serum also contained strong iso-hæmolysins, anti-A to a titre of 64, anti-B to a titre of 4. Approximately four years later, when her second pregnancy was of eight weeks' duration, the anti-A titre still had not returned to the level found at the eighth week of her first pregnancy, but was 2000. It slowly dropped as the second pregnancy progressed and was 500± at the delivery of a group A child, on whose blood a Coombs test produced a negative result. The anti-A titre on the sixth day after delivery had risen to 2000.

The results of serological investigations during these two pregnancies are shown in Table I.

On November 28, 1950, Mrs. W.P. attended the ante-natal clinic of the Queen Victoria Hospital, with her third pregnancy, estimated at nine weeks' gestation. At this stage of her pregnancy and at frequent intervals subsequently, her anti-A and anti-B agglutinin titres, of both the complete and incomplete types, were estimated. As is shown in Table II, there was a sharp rise in anti-A titre, particularly of the incomplete antibody, between the thirty-third and the thirty-seventh weeks of pregnancy. Mrs. W.P.'s previous obstetrical history, together with the rise of anti-A titre, was considered by the clinician as an indication to induce labour and perform an exchange transfusion. She was brought to hospital twelve days before term. Next day (June 27, 1951) she was delivered of a living female infant, weighing five pounds eight ounces, in whose cord blood the hæmoglobin value was 90% (12·6 grammes per 100 millilitres). The baby was only very slightly icteric at birth, but the jaundice could actually be seen to deepen during the preparation for the exchange transfusion. The child was of blood group A, Rh-positive, and was later found to be a secretor. The direct Coombs test on the cord blood produced a negative result, and there were no complete anti-A or anti-B agglutinins in the cord serum, but incomplete anti-A agglutinins were demonstrable to a titre of 8. Examination of a film of the blood disclosed the presence of approximately 56,000 nucleated red cells per millilitre.

An exchange transfusion was performed by the umbilical route, "Polythene" tubing 2·5 millimetres in diameter being used; the blood volume was estimated on the basis of 45 millilitres per pound of body weight; twice this amount *plus* an extra 100 millilitres was replaced in 10 millilitre amounts. This procedure occupied two hours, and the infant, which had shown rapidly progressive jaundice, entirely lost its icteric colour and exhibited a healthy pink tinge. The jaundice did not return.

The blood used for the transfusion had been taken half an hour previously from a healthy male donor, whose blood group was O, Rh-negative, with low anti-A and anti-B titres; the hæmoglobin content of the donor's cells was estimated at approximately 15 grammes per hundred millilitres; 3·8% citrate solution was added in the proportion of one part to four parts of the blood, and no attempt was made to concentrate the cells. At the conclusion of the transfusion, five millilitres of a 5% solution of calcium gluconate were given to the infant to counteract the effects of the citrate in the donor's blood, and one millilitre of vitamin *K* analogue ("Synkamine") was given into the umbilical vein. The infant withstood the procedure without any ill effects.

A sample of blood taken from the baby at the end of the operation was group O, Rh-negative, and the serum was shown to contain complete anti-A and anti-B agglutinins of the normal adult type, but no incomplete immune antibodies. The serum bilirubin level was 2·5 units per millilitre. The maternal serum at delivery gave the same titration figures as the sample taken on June 5, 1951, and no complete or incomplete anti-bodies acting on Rh_2, Rh_1 containing Cw, M, S, Kell-positive, Kell-negative, Le^a-positive, Le^b-positive, P-positive, P-negative, Duffy-positive or Duffy-negative cells could be demonstrated. The same results were obtained on a sample collected five days later. In Mrs. W.P.'s milk, collected ten days after delivery, the anti-A and anti-B complete agglutinin titres were 120 and 4 respectively. No incomplete antibodies were demonstrable.

Other Investigations.

In a study of the protective factors in heterospecific pregnancy and their role in the prevention of hæmolytic disease of the newborn, Tovey (1945) gives at least four possible mechanisms which could protect fœtal red cells against maternal antagonistic antibodies of the A B O systems: (i) lack of permeability of

TABLE II.

Serological Data Concerning Mrs. W.P.'s Third Pregnancy.

Time of Test.	Mother. Iso-Agglutinin Titre. Complete (Saline). Anti-A_1.	Anti-A_2.	Anti-B.	Incomplete. Anti-A_1.	Anti-A_2.	Anti-B.	Mother. Iso-Hæmolysin Titre. Anti-A_1.	Anti-A_2.	Anti-B.	Child.
1.5.51	120	32	8	64	Trace	Nil	++	±	Nil	
8.5.51	120	32	8	64	Trace	Nil	+++	++	Nil	
5.6.51	500	64	8	1,000	Trace	Nil	++++	++	Nil	
24.6.51 (Delivery)	500	250	16	1,000	Trace	Nil	++++	++	Nil	At birth: A R_1r, Coombs test negative result; cord serum, incomplete antibodies present; titre: anti-A_1, 8; anti-A_2, nil; anti-B, nil. After exchange transfusion with O Rh-negative blood: O Rh-negative, Coombs test negative result; complete agglutinating antibodies; titre: anti-A_1, 2; anti-A_2, nil; anti-B, 8.
After delivery. Sixth day	500	250	16	1,000	Trace	Nil	++++	++	Nil	
Twenty-third day										A Rh-positive; secretor.

the human placenta to anti-A and anti-B agglutinins; (ii) neutralization of incompatible anti-A and anti-B agglutinins crossing the placental barrier by group-specific substances in the fœtal plasma; (iii) lack of sensitivity of the fœtal red cells to the incompatible agglutinin; (iv) low activity of anti-A and anti-B agglutinins at body temperature.

It was thought of interest to attempt to estimate how far these mechanisms were effective against the incomplete antibodies in Mrs. W.P.'s serum, as Tovey's work was concerned with the complete antibodies only. The most readily investigated is the diminished activity of the agglutinins at body temperature; but on this point the protective mechanism breaks down, since like all immune blood group antibodies, the incomplete anti-A agglutinin was very active at 37° C.

Relative insensitivity of fœtal red cells is associated with the presence of group-specific substances. Thus when serum W.P. was titrated with cord blood group A cells, a titre of 120 for the normal agglutinins was obtained, as compared with a titre of 500 with adult cells. When the non-agglutinated cord cells in the higher serum dilutions were submitted to the indirect Coombs test, a positive result was found to a titre of 1000, a figure identical with that obtained in titration with adult cells, showing that, so far as the immune antibody is concerned, the sensitivity of cord cells is almost fully developed. However, the picture is different if the saline anti-A and anti-B agglutinins are removed from serum W.P. by the addition of equal parts of A and B substance; sensitization of adult cells can be shown to occur in a dilution of one in 500 of this mixture (that is, a serum dilution of one in 1000), but only a trace of sensitization of cord cells could be demonstrated in the undiluted mixture. These findings suggest that the addition of A and B substances in the abovementioned amounts has no effect on the interaction between incomplete antibodies and adult cells, but greatly interferes with the interaction of these antibodies with cord cells. However, larger amounts of A and B substances will also affect the incomplete antibody-adult cell linkage.

The next point to consider is the degree of permeability of the human placenta for blood group antibodies. It is difficult to assess serologically in the case of Mrs. W.P. how much antibody did pass the placental barrier, but there was strong evidence that some reached the fœtal circulation. Although the Coombs test on the cord cells gave a negative result, the child's hæmoglobin level was only 12·6 grammes per 100 millilitres, which seems to indicate that some damage to the fœtal red cells had occurred. It is possible that the incomplete antibody had passed the placenta, and that part of it was neutralized by the group-specific substances, as in our in-vitro experiment, while part was fixed to and destroyed some of the red cells, thus lowering the child's hæmoglobin level. Since the Coombs test result was persistently negative, the antibody liberated from the destroyed red cells did not apparently reattach itself to other red cells, but was, presumably, absorbed by the receptor substances of the plasma.

Comment.

It seems from these observations that even in cases of development of immune anti-A or anti-B antibodies, certain protective mechanisms still function, but less effectively than against the complete antibodies. We have, however, considered these mechanisms only in their action on red cells. The degree of fixation on other tissue cells may be of a different order, and it is possible that kernicterus and other damage to the developing fœtal organs is more likely to result from A B O sensitization than is anæmia. Wiener (1949) states that in 14 families with typical serological and clinical findings of *erythroblastosis fœtalis* due to A-B sensitization, which were investigated by him, there was a remarkably high incidence of cerebral sequelæ.

Serologically, the narrowness of the immunological response in our case is interesting. We have observed previously that in group O mothers pregnant with a group A fœtus, and with a pronounced rise in complete anti-A titre, there is often also a moderate rise in the anti-B titre. However, in this case, so far as the incomplete antibody was concerned, the rise in titre could be demonstrated only against A_1 cells.

When last examined the child was seven months old. Her progress was interrupted by the aspiration of some vomitus on the third day, but subsequently was clinically satisfactory whilst the infant was in hospital, and no abnormal signs have since been observed at frequent visits to the follow-up clinic in the out-patient department. She was breast fed. A blood sample, tested twenty-three days after the exchange transfusion, contained group A, Rh-positive cells.

We cannot offer any explanation why Mrs. W.P.'s first and third children were affected, the first one showing the very severe manifestations of kernicterus, and why the second child escaped. The serological picture of all pregnancies, as expressed in the rise of titre and development of hæmolysins and incomplete antibodies in the first and third pregnancies, and the fall in titre in the second, corresponded with the clinical outcome.

Summary.

1. The possible effects of A B O incompatibility between mother and child, with regard to damage to the child, are discussed.

2. The serological and clinical features are described of a case in which a mother belonged to blood group O and her three children to blood group A. The first child died of severe *erythroblastosis fœtalis*, including kernicterus; the second was clinically normal; and the third had a moderate degree of anæmia and jaundice shortly after birth, but progressed well after an exchange transfusion.

Acknowledgements.

We should like to thank the patient, Mrs. W.P., for her ever-willing cooperation, and Dr. Elsie Abrahams and her staff in the Pathology Department of the Queen Victoria Hospital for performance of blood counts and bilirubin estimations.

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CHRONIC RHEUMATIC (RHEUMATOID) MONARTHRITIS.

By MICHAEL KELLY,
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> The terms white swellings, scrophulous joints, etc., have been used without any well-defined meaning, and almost indiscriminately; so that the same name has been frequently applied to different diseases, and the same disease has been distinguished by different appellations. (Benjamin Brodie, 1822.)

CHRONIC RHEUMATISM is the commonest cause of intractable arthritis of a single joint, whether in adults or in children. Any opposition to this statement is more likely to be against the free use of the term rheumatism than against the proposition that chronic non-specific arthritis of a single joint is more common than chronic infection of a single joint. Many of us dislike to call a joint rheumatic in the absence of other signs of rheumatism (rheumatic fever, carditis, chorea, rheumatoid arthritis, multiple osteoarthritis). In our efforts to come to grips with the subject, we are hampered by the fashion which holds that rheumatism, as a constitutional disorder, should have systemic manifestations. When a single joint is involved, custom seldom permits us to speak of chronic rheumatism of one joint—rheumatic monarthritis.

For a localized manifestation we tend to look for local causes, such as infection or injury, and we speak of traumatic or infective arthritis. We do not always distinguish clearly between chronic bacterial infection of a joint (for example, tuberculosis) and the arthritides which are secondary to acute infections (urethritis, pharyngitis, dysentery, meningitis). These infections—and indeed almost any infection—may precipitate monarthritis or polyarthritis, or almost any rheumatic disorder; but they are not infectious in the same sense as tuberculosis is infectious, for the joint is not invaded by the causative organism.

If no such cause for the monarthritis is visible, many of us still cling to "infective", and we are often tempted to strain the rules of evidence in our efforts to incriminate a focus of infection. In other instances we use labels which give the status of a "clinical entity" but take no account of rheumatism—intermittent hydrarthrosis, periarthritis of a shoulder, osteochondritis, osteoarthritis of a hip, chronic sprain of an ankle, foot-strain, metatarsalgia.

Chronic monarthritis is more common than chronic polyarthritis. Because of its multiplicity of causes—and because of its varying clinical picture from case to case and from joint to joint—its essential unity is lost on us. When a number of patients are followed through the years, however, many of them will be found later to develop other rheumatic troubles. This is quite as likely when the monarthritis has been precipitated by trauma or specific infection as when it was apparently uncaused. Moreover, many patients with rheumatoid polyarthritis will on close questioning recall that they had suffered from painful swelling of a single joint earlier in life.

Reports of Cases.

In most cases the monarthritis clears up completely after many weeks or months, or it leaves only a slight trace, such as a crepitant knee or a mildly stiff shoulder. However, most of the following cases have been selected because they show that the rheumatism is quite likely to return—after a variable latent period—to the same joint or to a different joint.

Case I.—Sister N.T., aged fifty years, who had had no previous rheumatic disease, developed painful swelling of the left ankle. She had been working hard on night duty, and in addition had been nursing her sick mother during the day. There was no other precipitating factor; her weight (11 stone 10 pounds) contributed to overstrain. After six weeks of ineffective treatment she was ordered off duty and made to rest at home. After a further six weeks the ankle had improved a little, though it remained slightly swollen and painful for several months.

Case II.—Mrs. I.M.R., aged fifty-one years, had injured her right knee eight months before (January, 1948), and it had remained swollen and painful. On examination it was distended and there was limitation of flexion and extension. The quadriceps was wasted. X-ray examination revealed no abnormality. The joint was restored to normal in three months by the application of a walking plaster cast, followed after its removal by gradual restoration of flexion. There has been no further joint disease. On being questioned, the patient said that her left knee had been painful and stiff (without swelling) for three months in 1945.

Case III.—Mrs. E.F.B., aged fifty-six years, has had painful stiffness of the left knee for two years. There is no swelling, but the knee is painful on walking downstairs or sitting in a low chair. More recently she has had slight pains (without visible change) in the right knee and in the wrists. Examination reveals limitation of flexion of the left knee by 30°, with crepitus. The X-ray film shows mild osteoarthritic lipping. On being further questioned the patient said that she had had fluid in the left knee thirty years before without apparent cause. She was nearly incapacitated for three years, finally spending a year in a public hospital.

Case IV.—A.V., when she was fourteen years old, suffered from swelling of her left knee. It was diagnosed as tuberculous and she spent two years in an orthopædic ward. After this she had no articular symptoms until she was aged twenty-one years, when her right subtalar joint was dislocated and lacerated in a motor-car accident. While she was in hospital being treated for this, the left knee became grossly distended; then the right wrist was involved; many large joints have been affected during the past three years.

Case V.—Mrs. A.McG., aged sixty years, has had mild twinges of rheumatism for twenty years. Five years ago the left knee became painful and swollen, and the condition would not subside. Two orthopædic surgeons diagnosed tuberculosis; she spent one year in an orthopædic ward and a year walking with the left leg in a weight-bearing caliper. When she left hospital pain and stiffness developed in the shoulders, wrists, fingers and right knee. The typical picture of rheumatoid arthritis developed.

Case VI.—J.B.M., aged twenty-three years, suffered from swollen left knee when he was two years old; it was treated for a year as tuberculous in a surgical ward at the Children's Hospital. No further joint trouble occurred for ten years, when the left knee swelled again. It was regarded by an orthopædic surgeon as tuberculous, and treated with a walking caliper for a year. For a further seven years there was no more trouble (though the left knee had a range of only 120° of movement); then pains were felt in various joints, and both knees swelled. They have remained so for two years; both elbows are also swollen and painful.

Case VII.—Mrs. M.G., aged forty-six years, had an operation for uterine prolapse four years ago. Ten days after the operation the left ankle became acutely swollen, and remained so for four months. Since then she has been subject to pains in many joints without swelling; her feet are especially sore. Further questioning revealed that she had hurt her left knee when she was nine years old, and it had been distended with fluid for many months. Subsequently she had had no serious trouble with it, though she was always conscious that it was weak.

Case VIII.—C.C., when aged nine years, fell and injured her left hip; it remained painful and she was lame for one year. The hip recovered, and a few weeks later the terminal joint of the left middle finger became grossly swollen. It alone remained swollen for eight months, while many investigations were carried out and many forms of treatment were tried. The joint was regarded as tuberculous until other finger joints became swollen. The wrists and the feet gradually became involved during the next three years. When she was aged fourteen years a complete remission was obtained by immobilization of all the involved joints in plaster of Paris for four weeks. She had no more rheumatism for three years, when she injured her right knee. It has been very painful, with decalcification and loss of cartilage, for eighteen months; six months ago the left hip, the wrists and the left ankle became involved. The hip is now stiff and she is continuously in bed.

Case IX.—Miss H.A., aged forty-nine years, has suffered from severe rheumatoid arthritis since 1941. She had not previously been a rheumatic subject, but in 1935 the proximal interphalangeal joint of the left index finger became swollen without apparent cause. The swelling subsided after three months and left no trace. In 1940 the right shoulder became painful and stiff, and remained so for several months. Then the left shoulder, elbows and wrists were involved, and few joints escaped.

Case X.—Miss M.A., aged sixty-five years, injured her left knee in a motor-car accident ten years ago. She recovered after a few months. Two years later the right wrist became painful and swollen when she was recovering from an attack of bronchitis. The wrist has remained painful ever since; now it is enlarged and swollen, with gross radiological changes. The knee is crepitant, but has a full range of movement.

Case XI.—Mrs. J.N., aged fifty-four years, says that her right knee became painful seven years ago, after a sore throat. It remained mildly painful, but not swollen, for six years. When the knee pain subsided the right shoulder became painful and stiff; six months later its range of movement had been reduced by 50%. X-ray examination revealed no abnormality. Under treatment the pain subsided and the range of movement gradually increased, though it is not yet normal.

Case XII.—L.F., aged thirty-five years, who was first examined in April, 1949, had had a painful swelling of the left wrist for three weeks. In 1945 and 1947 the same wrist had swelled for a few weeks each time. The only history of injury was a fracture of this wrist when he was ten years old. From 1943 onwards swelling of the left knee had appeared and subsided several times, never at the same time as the wrist. In 1946 an operation was performed for removal of a loose body in the knee joint. X-ray examination of the wrist revealed no abnormality. The swelling subsided after the joint had been for three weeks in plaster of Paris, and left some residual thickening of the wrist.

CASE XIII.—I well remember in the army a soldier who recovered from cerebro-spinal meningitis, but whose knee was held fixed in extension, and great pain was felt on any attempts to move it. The swelling was mainly periarticular, but the bone ends rapidly became decalcified and the cartilage disappeared. Tuberculosis was suspected but never proved. The joint was arthrodesed after four months; the later history of the soldier is not known.

CASE XIV.—In a similar, more recent case, a woman, aged fifty years, had had an extremely painful left knee for four years without known cause. Arthrodesis was performed; within a few weeks of the operation several joints became swollen for a time; in the right knee a persistent condition developed resembling that of the left.

CASE XV.—Mrs. D.C.H. has been suffering from severe rheumatoid arthritis for six years. Many joints are swollen and deformed and she spends most of her time in a wheel chair. She said that her rheumatism really commenced 22 years ago, when the right knee swelled. After this the same knee swelled and subsided several times. Six years ago it swelled again and did not subside; soon the left knee and many joints were involved.

THE SIGNS OF ARTHRITIS.

Since student days we have been told that pain, stiffness and swelling of a joint are the signs of arthritis. A knee, ankle or wrist joint which remains painful and swollen after an injury is said to be affected by traumatic arthritis; after dysentery it is called dysenteric arthritis; after urethritis it is called Reiter's syndrome; and so on. When a joint swells without apparent cause in a patient who has had other rheumatic troubles, we agree to call it rheumatic. In the absence of a rheumatic history, we know not what to call it.

But this is not our sole difficulty in making use of the term arthritis. When the shoulder, the elbow or the hip is involved, swelling is not normally visible to the eye; and so we hesitate to use the term arthritis unless X-ray signs can be seen. But X-ray signs are not common in the shoulder, which can secure comparative rest when it is painful. Thus we seldom diagnose arthritis of the shoulder even when it is painful and fixed, with profound muscular wasting. We prefer to call it frozen shoulder, or periarthritis, when every clinical indication and every rule of logic suggest that we should call it arthritis of the shoulder.

The present series of 15 patients contains eight instances of arthritis of the knee, and in four others a knee had given trouble before. The knee was involved in eight out of thirteen cases of monarthritis reported by Kuhns (1945) and in nearly half of the known cases of monarticular trauma which progressed to polyarthritis (Kelly, 1951*b*). It is affected more commonly than other joints for two reasons: (i) The signs of arthritis are more compelling (large distended synovial cavity, clearly visible). (ii) When the signs have appeared, they do not settle down so readily because the knee is normally subjected to greater strain than other joints.

INTERMITTENT HYDRARTHROSIS.

Recurrent distension of the knee-joint was called intermittent hydrarthrosis by Moore (1867). At times attempts have been made to explain it upon an allergic basis (Bierring, 1921; Miller and Lewin, 1924; Berger, 1939). A biopsy of the synovial membrane showed changes exactly like those of rheumatoid arthritis (Porter and Lonergan, 1936). It may occur after brucellar and other infections (Sharpe, 1936). Ropes and Bauer (1945) have shown that intermittent hydrarthrosis may develop into a typical picture of rheumatoid arthritis. This is what happened in Cases IV, VI and XV, in which intervals of several years separated the earliest attacks of hydrarthrosis.

But hydrarthrosis is not always the most prominent feature of chronic arthritis of the knee. In Cases VIII, XIII and XIV decalcification of bone caused a picture like that of post-traumatic osteoporosis. Distension may not occur if the movements are prevented by protective spasm. There is every degree of gradation between gross distension of a freely mobile joint and a fixed and painful atrophic joint.

DIFFERENTIATION OF CHRONIC RHEUMATISM FROM TUBERCULOSIS.

When decalcification of bone is patchy—and for various other reasons—it may be difficult to differentiate rheumatic arthritis from tuberculosis. In Cases IV, V, VI and XIV the patients received prolonged hospital treatment for tuberculosis and the true diagnosis did not become evident for several years. Waugh (1951) recently described an instance similar to Case XIV: after arthrodesis had been performed on a painful and swollen knee, many joints became involved, with decalcification of bone ends and patchy sclerosis.

Of Kuhns's 13 cases, six were provisionally diagnosed as tuberculous, but in only three was the diagnosis confirmed by transference of infection to animals. A biopsy may lead us astray, for chronic rheumatic tissues may contain giant cells, believed by many to be diagnostic of tuberculosis. Two recent writers have exemplified these diagnostic difficulties in the wrist (Miller and others, 1950) and in the shoulder (Meyerding and Ivins, 1948). Several writers have pointed out that chronic rheumatic monarthritis is not uncommon in children and that it should be carefully differentiated from tuberculosis (A. D. Smith, 1932; Collins and Cameron, 1936; Pickard, 1947; Lockie and Norcross, 1948). In Cases IV, VI and VIII of the present series the arthritis commenced in childhood and was thought to be tuberculous.

Brocher (1949) also discussed the differentiation of monarticular arthritis from tuberculosis. In reporting a case of recurrent monarticular arthritis of the elbow, however, he fell into the prevalent error of avoiding the term "rheumatic". On the doubtful evidence of a prolonged coagulation time he called it hæmophilic, though his thirty-four year old patient had no family history of hæmophilia and had never had any hæmorrhages or other joint troubles.

THE PRECIPITATING FACTOR.

In 10 of the 15 cases precipitating factors played a part, as follows: Case I, overstrain; Case II, injury (second attack); Case IV, injury, operation, infection (second attack); Case V, generalized fibrositis; Case VII, operation (second attack); Case VIII, injury (first and third attacks); Case X, injury (first attack), infection (second attack); Case XI, infection (first attack); Case XIII, infection; Case XIV, operation (second attack).

In five of these the first appearance of rheumatic disease was precipitated by infection or by injury to the joint which became involved. In precipitating the later attacks the same factors seemed to play a part. In Cases VII and XIV surgical operations brought on the second attack, and in Case IV the knee flared up for the second time while a lacerated wound of the opposite foot was under treatment.

Whether rheumatism is localized or generalized, in a little more than half of the cases it appears without obvious cause, and in nearly half it is precipitated by tissue damage or infection. Thus the list of precipitating factors in these few instances of localized rheumatism is what we should expect.

Of Kuhns's 10 cases not proved to be due to tuberculosis, three were precipitated by injury and two by acute infections. In one the condition commenced acutely and was diagnosed as gonococcal on the doubtful evidence of a positive response to the complement fixation test. In four it was gradual in onset; in two of these the condition was diagnosed finally as probably tuberculous, in one as hysteria and in one as rheumatoid arthritis. Of those conditions caused by injury, one was diagnosed as chronic sprain, one as rheumatoid arthritis, and one as probably tuberculous. Thus does the multiplicity of our approach to this disorder lead us astray and prevent us from considering it as a unit.

In several large series of cases of polyarthritis we find that the same list of causes—infection, operation and trauma—is responsible for two-fifths of the cases (M. Smith, 1932; Edström, 1942; Finney and others, 1947; Short and others, 1949; Cecil and Kammerer, 1951).

Non-Tuberculous Infection.

Kuhns labelled two of his cases "infectious" because the condition followed sore throat. However, there was no evidence that the joints themselves were infected by streptococci or other organisms. Infection acted as a precipitating factor in Cases XI and XIII, and in Case X acute bronchitis brought on the second attack of arthritis. Freeman (1935) has written as follows:

> We have abundant evidence that infections can give rise to rheumatic symptoms, and that practically every infection can produce them on occasion. Rheumatism may be regarded as one of the possible sequelæ of invasion by foreign organisms.

Some organisms (for example, the gonococcus and *Micrococcus melitensis*) are more prone than others to give rise to chronic rheumatic sequelæ, but the organisms can rarely be recovered from the joint. There is no evidence that bacterial toxins have any special effect on articular tissues. The infections act in the same way as other instances of damage to tissues; thus surgical operations—without infection—are not an uncommon cause of monarthritis (Cases VII and XIV) and polyarthritis (M. Smith, 1932).

The Influence of Trauma.

It is not easy to assess the true role of trauma. A normal joint recovers from traumatic synovitis; the failure of the injured joint to recover can be attributed to three factors: (i) over-use of the injured joint, (ii) disturbed joint physiology, (iii) constitutional factors.

Over-use of the Injured Joint.

Physiological use of a painful and swollen joint imposes a strain on it, and any movement of inflamed synovial tissues amounts to trauma. Thus a vicious circle may set in, but most injured joints recover even when used a good deal; another factor—disturbed joint physiology—is required to maintain the diseased state (Bennett, 1943). In the hypersecretion of fluid disturbed reflexes play a large part (Leriche, 1928; Cotton, 1933). This change takes a few weeks to develop (Doub, 1933); it is especially likely to occur if the trauma is repeated (Archer, 1935).

Disturbed Joint Physiology.

Chronic monarthritis, though a localized disorder, indicates a disturbance of the whole organism, for, as we have seen, it is frequently brought on by systemic disease. It may be precipitated by infection or by operation, or by anything which causes appreciable damage to any non-articular tissues. A systemic change is brought about which initiates a joint disorder that resembles the effects of injury. And then normal movements of the joint constitute trauma to the already damaged tissues. The chronic arthritis tends to perpetuate itself.

The Constitutional Factor.

Hortling (1949) has reported an interesting case of pituitary deficiency, in which an injury to the knee was followed by severe monarthritis with ankylosis. Here we have the systemic factor acting locally to intensify the effects of injury; another instance is the neuropathic (Charcot's) joint, in which changes like those of trauma are due chiefly to disturbed reflexes.

The constitutional change itself, it appears, may be initiated by articular damage, for injury to a single joint may bring on polyarthritis in old patients, with no family history of rheumatism, who have never had rheumatism before (Kelly, 1948, 1951*b*). In Case X traumatic monarthritis of the knee subsided after a few months but was followed in a year by arthritis of the wrist. In Cases IV, VI, VIII, XIV and XV recurrent monarthritis later progressed to polyarthritis.

The spread from one to many joints also depends on the constitutional factor. There is no means of distinguishing the patient who will develop polyarthritis from the patient who will not. Much evidence suggests that the spread is guided by nervous reflexes (Kelly, 1948, 1949, 1951*a*, 1951*b*). In chronic rheumatic monarthritis the pathological changes are exactly like those of chronic polyarthritis; but they are confined to a single joint.

Rheumatoid monarthritis differs from polyarthritis in the same degree that a furuncle differs from furunculosis. The existence of multiple lesions does not suggest or indicate a profound change in the nature of the disorder—it merely means that some (perhaps neural) factor is making the same process spread from joint to joint.

Treatment.

Treatment is not the subject of this article. One or two aspects of treatment, however, support my thesis that rheumatic inflammation is essentially one disorder despite its multiplicity of precipitating factors.

1. Cortisone. Cortisone suppresses all forms of chronic rheumatic inflammation, whether apparently uncaused or due to precipitating factors. This indicates that rheumatic inflammation is a single form of tissue change despite the multiplicity of clinical pictures.

2. Immobilization. Rheumatic inflammation in any joint may be completely suppressed by continuous immobilization. Ankylosis does not occur, and a remarkable range of movement can be restored if the correct technique is followed. Furthermore, when a number of joints are involved, immobilization of the one most severely affected often leads to a remarkable improvement in the others.

Conclusion.

My thesis is that rheumatism is a pathological if not a clinical entity, and it signifies non-specific inflammation of mobile fibrous tissues. Whether apparently uncaused, or precipitated by infection, injury or other disorders, it should still be called rheumatic. We tend to forget the simple fact that rheumatic inflammation is essentially a response to movement. If our forefathers had called it the "movement-disease" (perhaps kinetosis) instead of the "humour-disease", we should understand a good deal more about the disorder today.

Summary.

1. Chronic rheumatism is the commonest cause of intractable arthritis of a single joint.

2. In more than half the cases it begins without apparent cause. In the remainder it is brought on by a number of precipitating factors.

3. Though the clinical picture varies from patient to patient and from joint to joint, the disorder is essentially one.

4. The clinical pictures are frequently given names which do not take into account their rheumatic nature.

5. Frequently the error is made of diagnosing articular tuberculosis, which is much less common.

6. Many of the patients suffer recurrence of the arthritis in the same or other joints, and many eventually progress to rheumatoid arthritis.

7. There is no essential difference between chronic rheumatic monarthritis and chronic polyarthritis.

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RESPONSE OF THE MALE TOAD, BUFO MARINUS, TO CHORIONIC GONADOTROPIN AND USE OF THE ANIMAL FOR BIOLOGICAL ASSAY.

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SINCE Galli-Mainini, in 1948, drew attention to the remarkably rapid and specific physiological phenomena associated with the injection of chorionic gonadotropin into male Batrachia, many papers have been devoted to such pregnancy tests with a wide variety of toads and frogs. Thorborg and Hansen have described the more recent work in their series of articles (Thorborg, 1950*a*, 1950*b*, 1951; Thorborg and Hansen, 1951), giving references which completely cover the previous literature.

On the matter of cost, simplicity of feeding and maintenance of the animals, it was natural that owing to the distinct advantages of this type of test over pregnancy tests which involve use of other animal species, interest should be centred in Batrachia found to be most prevalent in the various local areas.

Thus, in England and on the Continent the possibilities of using *Bufo bufo* and *Rana esculenta*, in South Africa *Xenopus lævis*, and in South America a large variety of the *Bufo* species, have been investigated.

Here, in Australia, the most common and easily obtainable toad appears to be the so-called Giant American Toad, *Bufo marinus*, whose introduction in 1935 by the Queensland Department of Agriculture has been fully recorded by Mungomery (1935).

Bettinger and O'Loughlin (1950) have described the clinical pregnancy test with *Bufo marinus* obtained from the North Queensland area, and it is understood that most laboratories throughout the Commonwealth now perform this test.

Whilst this technique, in parallel with the Aschheim-Zondek, has been used for some time at this School, it was felt that more quantitative information regarding the dose-response relationship of human chorionic gonadotropin with male *Bufo marinus* was desirable.

As this did not appear to be available in current literature, an investigation was instituted with a quantity of internationally standardized human chorionic gonadotropin ("Prolan") obtained from Bayer Pharma, Proprietary, Limited.

Experimental Methods.

Preliminary Approach.

From graphic information available (Harrow, 1946; Wilson, Albert and Randall, 1949; Albert, 1948) regarding the excretion levels of human chorionic gonadotropin over the pregnancy period, it appears that up to one month, and also from four months onwards, concentrations of the order of 10 international units or less per millilitre of urine are usual.

The amount to be injected in 10 millilitres therefore should range from 100 international units down.

Small groups, varying in number, of toads were selected at random from a batch of 48 animals of varying size and given the amounts, 100, 50, 40, 30, 20 and 10 international units, each dose being in a volume of 10 millilitres of distilled water. The results obtained are set out in Table I.

The results indicated that by selecting doses ranging somewhere between 10 and 40 international units and reading the test after four hours, a response range of approximately 10% to 90% of the animals might be expected.

Biological Assay.

To facilitate statistical treatment of results, doses selected at equal logarithmic intervals (8, 12, 18, 27 and 40·5 international units) were given, as described below, to five groups of animals on the same day.

The importance of testing all animals on the same day has been stressed by Emmens (1950).

Ninety male specimens of *Bufo marinus* received from North Queensland, when tested individually with 40 international units of "Prolan", were all found to spermiate.

Seven days were allowed to elapse after the test injection of 40 international units, then the urine from each of the 90 toads was examined for residual spermatozoa. None was found.

These toads were then selected at random into five groups, each of eighteen individuals, and called the "O1" series.

O1*a* consisted of 18 individuals each given eight international units of "Prolan".
O1*b* consisted of 18 individuals each given 12 international units of "Prolan".
O1*c* consisted of 18 individuals each given 18 international units of "Prolan".
O1*d* consisted of 18 individuals each given 27 international units of "Prolan".
O1*e* consisted of 18 individuals each given 40·5 international units of "Prolan".

TABLE I.

Toad.	Weight. (Grammes.)	Dose and Date.	Result Read at: Two Hours.	Four Hours.	Twenty-four Hours.	Toad.	Weight. (Grammes.)	Dose and Date.	Result Read at: Two Hours.	Four Hours.	Twenty-four Hours.
1	85	100 I.U., 1230 hours, 4/4/51.	+	+	+	25	75		+	+	+
2	90		+	+	+	26	75		+	+	−
3	125		+	+	+	27	85		+	+	+
4	50	50 I.U., 1230 hours, 4/4/51.	+	+	+	28	90		−	+	+
5	60		+	+	−	29	95		+	+	+
6	65		−	+	−	30	90	30 I.U., 1045 hours, 11/4/51.	+	+	−
						31	90		−	+	+
7	85	50 I.U., 0930 hours, 6/4/51.	+	+	+	32	90		+	+	+
8	90		+	+	−	33	85		+	+	+
9	75	40 I.U., 0930 hours, 6/4/51.	+	+	−	34	80		+	+	+
10	80		+	+	+	35	70		+	+	−
11	70	30 I.U., 0930 hours, 6/4/51.	−	+	−	36	80		+	+	−
12	75		−	+	−						
13[1]	110	30 I.U., 1200 hours, 9/4/51.	−	−	−	37	75		+	+	+
14	85		−	+	−	38	75		+	+	+
15	75	20 I.U., 1200 hours, 9/4/51.	+	+	−	39[1]	70		−	−	−
16[1]	100		−	−	−	40	60		+	+	+
17[1]	80	10 I.U., 1200 hours, 9/4/51.	−	−	−	41[1]	65		−	−	−
18[1]	85		−	−	−	42[2]	35	20 I.U., 1145 hours, 16/4/51.	−	−	−
						43	85		−	+	+
19	65	30 I.U., 0915 hours, 10/4/51.	+	+	+	44	80		+	+	+
20	60		+	+	−	45	65		+	+	+
21	80		+	+	+	46	75		+	+	−
22	70		+	+	+	47	60		+	+	+
23	70		+	+	+	48	80		−	−	−
24	75		+	+	+						

[1] These animals subsequently reacted when tested with a dose of 50 international units.

[2] This animal failed to react subsequently to doses of 50 and 100 international units; post-mortem examination and histological section showed it to be a male.

Specimens of urine from the groups were examined microscopically four hours later for the presence or absence of spermatozoa.

After a seven-days interval the urine of all animals was reexamined for residual spermatozoa. None was found.

During this period one animal had died, leaving a total of 89. These were mixed in a large cage and a further series ("O2") of five groups (four of 18 individuals and one of 17 individuals) was picked at random and the experiment repeated as before with the same scheme of dosage.

After a further seven-days interval, during which several toads expired, another series ("O3") consisting of five groups, each of 16 individuals, was selected at random and the tests were repeated once more.

Results of these tests are given in Table II.

During these experiments a new batch of 74 animals was received. These were kept separately from the "O" series and no initial testing dose of chorionic gonadotropin was given.

"N1" series, as these animals were termed, was divided into five groups (four of 15 individuals and one of 14 individuals) and experiments were conducted on identical lines to those of the "O" series. Seven-day intervals having been allowed before regrouping, two more series ("N2" and "N3") were selected at random and tested. Routine microscopic examination of the urine on the day prior to testing failed to reveal any residual spermatozoa.

The results are presented in Tables II, III and IV.

Just after commencement of the "O3" series it was thought that by recording the number of animals still "positive" at the twenty-four hour and forty-eight hour periods some information might be obtained regarding the time during which spermatozoa were still being eliminated in the urine.

The percentage of toads in the two series giving positive reactions are set out in Table V.

Observations

Rate of Elimination of Spermatozoa.

During tests carried out with pregnancy urine specimens prior to the present investigation, it was observed that maximum elimination of spermatozoa appeared twenty-four hours after injection and that they could be demonstrated microscopically in small numbers for periods up to ninety-six hours.

In the present experiments with "Prolan", maximum elimination appeared more rapidly—four hours after injection—whilst much smaller numbers were to be seen at the end of twenty-four hours and forty-eight hours, and nearly all specimens of urine were microscopically free of spermatozoa at the end of seventy-two hours. This observed difference in behaviour may be due to: (i) the effect of higher levels of chorionic gonadotropin in the pregnancy urine specimens—that is, higher concentration than the "Prolan" doses given in the experiments; (ii) a possible retarding effect (delaying absorption of the chorionic

TABLE II.

Dose of "Prolan" (I.U.).	Group.	O1 Series. Number of Animals.	O1 Series. Number Positive.	O2 Series. Number of Animals.	O2 Series. Number Positive.	O3 Series. Number of Animals.	O3 Series. Number Positive.	N1 Series. Number of Animals.	N1 Series. Number Positive.	N2 Series. Number of Animals.	N2 Series. Number Positive.	N3 Series. Number of Animals.	N3 Series. Number Positive.
8	*a*	18	1 (5·56%)	18	2 (11·11%)	16	1 (6·25%)	15	1 (6·67%)	15	1 (6·67%)	15	3 (20·00%)
12	*b*	18	4 (22·22%)	18	5 (27·78%)	16	4 (25·00%)	15	2 (13·33%)	15	3 (20·00%)	15	4 (26·67%)
18	*c*	18	12 (66·67%)	18	10 (55·56%)	16	6 (37·50%)	15	8 (53·33%)	15	9 (60·00%)	15	10 (66·67%)
27	*d*	18	12 (66·67%)	18	14 (77·78%)	16	6 (37·50%)	15	10 (66·67%)	15	11 (73·33%)	15	9 (60·00%)
40·5	*e*	18	16 (88·89%)	17	17 (100·00%)	16	16 (100·00%)	14	12 (85·71%)	14	12 (85·71%)	13	12 (92·31%)

gonadotropin) by substances present in pregnancy urine specimens.

Weight of the Animal.

At the commencement of the experiments a careful check was kept on each individual toad to determine whether weight was significant to the response. This was abandoned when it became obvious that whilst some of the smaller toads failed to respond to the largest dose, some of the larger toads did react to the smallest dose given.

TABLE III.

Summary of Results for Data in Table II.

Series.	Slope.	Mean Slope ± Standard Error.	Median Effective Dose.	Common Median Effective Dose ± Standard Error.
O1	3·75±0·69	3·67±0·30	3·019±0·230	3·046±0·1015
O2	4·37±0·77		2·741±0·275	
O3	3·65±0·74		3·457±0·256	
N1	3·83±0·78		3·273±0·254	
N2	3·64±0·75		3·049±0·261	
N3	2·90±0·70		2·811±0·313	
	($\log_{10}$ slope)		($\log_{1·5}$ M.E.D.)	

5% fiducial limits of slope are 3·67±(0·30×1·96), that is, 3·08 and 4·25.

5% fiducial limits of median effective dose ((0·5014) and (0·5714)) 8/1·5, that is, 16·9 international units and 19·8 international units.

Mean median effective dose=18·3 international units.

TABLE IV.

Partitioning of χ^2 for Data of Table III.

Source of Variation.	Degrees of Freedom.	χ^2.	P.
Parallelism	5	2·5960	0·7–0·8
Heterogeneity	16	17·7790	0·3–0·5
Total	21	20·3750	

Pre-testing of Animals.

It will be noted that although all the individual toads in the "O" series reacted when pre-tested with 40 international units of "Prolan", two of these toads selected at random in the "O1*e*" group failed to respond later to 40·5 international units. Such biological variation suggests that for pre-testing, in order to obtain a 100% response, at least 2·5 times the median effective dose (that is, approximately 50 international units for *Bufo marinus*) should be given (compare Thorborg and Hansen, 1951), and that when one is dealing with specimens suspected of low chorionic gonadotropin concentration it is advisable to use at least two toads simultaneously in the Bettinger and O'Loughlin test.

Comparison of the pre-tested ("O") with the non-pre-tested ("N") series shows that pre-testing did not affect the slope (see Table IV).

Relative Sensitivity of Bufo Marinus.

Comparative degrees of sensitivity of animals used in the various pregnancy tests are shown by Table VI.

Under the conditions of the tests, male *Bufo marinus* would appear to be approximately one-half as sensitive as the female rabbit.

Consequently, when one is testing specimens suspected of having a high concentration of chorionic gonadotropin, it should be equivalent to use male *Bufo marinus* with urine dilutions of 1:5, 1:50 and 1:100 in place of the usual Friedman test with urine dilutions of 1:10, 1:100 and 1:200.

Seasonal Variation.

Seasonal variation has been found to influence certain *Bufo* species (Thorborg and Hansen, 1951). However, Lima and Pereira (1948) found that keeping *Bufo marinus* at low temperature (9° C.) did not affect the response.

In the "Prolan" experiments the toads were used over the period April to November, and during this time (beginning of autumn to the next summer) no great differences were shown in the responses.

Response of Fasting Male Bufo Marinus.

Ninety animals which had been fasting for at least three months were selected at random into three groups, each of 30 individuals, which were given 12, 18 and 27 international units of "Prolan". Results are shown in Table VII. These indicate that even with animals which have fasted at least three months, the dose response curve does not alter significantly.

Summary.

1. Experiments have been conducted to determine the dose-response relationship of chorionic gonadotropin in the male toad *Bufo marinus*.

2. The mean median effective dose of chorionic gonadotropin has been estimated to be 18·3 international units, with 5% fiducial limits of 16·9 and 19·8 international units.

3. The toads can be used repeatedly, with seven-day intervals between testing, without their sensitivity becoming impaired.

4. Although small numbers of spermatozoa very soon appear in the urine, maximum elimination appears at the end of four hours with a commercially prepared human chorionic gonadotropin ("Prolan") and at the end of twenty-four hours with normal pregnancy urine specimens.

5. Persistence of spermatozoa in the urine for periods up to three days after injection of "Prolan" and for periods up to four days after injection of normal pregnancy urine specimens has been observed.

6. In the mature male *Bufo marinus*, weight, seasonal variations, fasting conditions and pre-testing with doses of chorionic gonadotropin do not adversely affect the response.

TABLE V.[1]

Results (Percentage Positive) at the Four Hour, Twenty-four Hour and Forty-eight Hour Periods.

Dose. (International Units.)	O1 Series.			O2 Series.			O3 Series.			N1 Series.			N2 Series.			N3 Series.		
	4 Hours.	24 Hours.	48 Hours.	4 Hours.	24 Hours.	48 Hours.	4 Hours.	24 Hours.	48 Hours.	4 Hours.	24 Hours.	48 Hours.	4 Hours.	24 Hours.	48 Hours.	4 Hours.	24 Hours.	48 Hours.
8	6	—	—	11	6	—	6	0	0	7	0	0	7	0	0	20	0	0
12	22	—	—	28	11	—	25	6	0	13	0	0	20	0	0	27	0	0
18	67	—	—	56	28	—	37	6	0	53	33	13	60	13	7	67	60	13
27	67	—	—	78	50	—	37	13	6	67	74	27	73	40	33	60	67	33
40·5	89	—	—	100	60	—	100	87	31	86	93	50	86	80	50	92	85	46

[1] The following is an approximate summary of data in Table V and generalizations from the readings: Dose of 8 international units: all animals "negative" at 24 hours. Dose of 12 international units: very occasional sperms at 24 hours, none at 48 hours. Dose of 18 international units: sperms at 24 hours, approximately one-sixth still "positive" at 48 hours. Dose of 27 international units: sperms at 24 hours, approximately one-third still "positive" at 48 hours. Dose of 40·5 international units: sperms at 24 hours, approximately one-half still "positive" at 48 hours.

TABLE VI.

Sensitivities of Animals in Detection of Chorionic Gonadotropin.

Test.	Animal and Weight.	Approximate Median Effective Dose.	Amount of Urine Injected. (Millilitres.)	Time of Reading. (Hours.)	Approximate Level Above Which Positive Result Obtained. (International Units per Millilitre.)
(1) Friedman	Female rabbit: 2 to 3 kilograms.	15	15	48	1
(2) Aschheim-Zondek	Immature female mice: 8 grammes.	10	2	100	5
(3) Hogben	Female toad, *Xenopus lævis*: 60 to 100 grammes.	70	7	24	10
(4) Galli-Mainini (male toad):					
(*a*) *Bufo bufo*	Male *Bufo bufo*: 15+ grammes.	8	1	6	8
(*b*) *Bufo arenarum*	Male *Bufo arenarum*: 100+ grammes.	40	10	3	4
(*c*) *Bufo marinus*	Male *Bufo marinus*: 45 to 125 grammes (mean 75 grammes).	20	10	4	2

7. The pregnancy test with the male toad *Bufo marinus* has been shown to be approximately one-half as sensitive as the Friedman female rabbit test.

TABLE VII.

Group.	Dose of "Prolan". (International Units.)	Result Read at		
		4 Hours.	24 Hours.	48 Hours.[1]
I	12	7/30=23%	2/30= 7%	—
II	18	15/30=50%	6/30=20%	—
III	27	25/30=83%	16/30=53%	—

[1] Readings not taken—many of the toads were dead or moribund.

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THE MECHANISM OF RESULTS IN TREATMENT WITH ACTH AND CORTISONE.

By W. J. McCRISTAL,
Sydney.

IN choosing the title for this paper I was tempted at first to qualify it with such terms as "possible", "probable", "an attempt to integrate" *et cetera*. Subsequently it was decided to throw down the gauntlet in the form of a challenge and use a somewhat provocative title, even though we are still at the crossroads whether to regard ACTH and cortisone as therapeutic agents or as research tools for the better understanding of physiology and disease. No one but a fool will deny their intellectual impact on the philosophical and scientific side of medicine. One of our most distinguished surgeons has confessed that he is engrossed in the study of ACTH and cortisone to the detriment of his daily bread; those of us in the winter of our career are envious of those on the threshold of theirs, in the thought that they will be sallying forth like the Argonauts of old to confound Philip Hench's dictum that the nature of the action of cortisone in rheumatoid arthritis is "a riddle wrapped in a mystery inside an enigma"; and cortisone and its parent ACTH are further honoured and ennobled in being associated with three Nobel Prize winners—Reichstein, Kendall and Hench. I wish to disavow any undue claim to originality. The references represent only a small portion of those availed of, and to those authors whom I have inadvertently omitted I express my apologies and indebtedness. In a field of medicine so much in a state of flux it is inevitable that difficulty will arise in sorting out fact and assumption, and in avoiding the issue of appearing trite between the time of writing and publication.

Whilst in some quarters, to wit, Dr. J. J. R. Duthie's paper "Rheumatic Diseases in U.S.A.", one finds trenchant, though just and constructive, criticism of undue claims for the adrenal steroids in the field of therapy, in others there is an insatiable tendency to confuse the real issue, namely, the physiological and pharmacological explanation of the ability of the adrenal hormones to reverse disease processes and thus inspire hope in our all too frustrated

breasts. Through the providence of available funds, scientific and clinical research in the United States of America in the adrenal steroids has had unlimited scope. Manufacturing houses in that country have used their resources and ingenuity at great capital risk and expenditure to produce a therapeutic principle from the animal, vegetable and synthetic kingdoms. Thus the impetus has been given the medical world to measure its wits with new working concepts of many diseases hitherto little understood. Through the toil and sweat of research workers in this field the veil of mental hebetude, crusty conservatism and despair has been lifted, at least temporarily, and churlish non-acceptance and lack of appreciation of the efforts of those responsible are to be deplored. It is not their fault if lesser people hitch on with semiscientific balderdash and bring detraction to the scene.

Trial therapy is often a useful tool in diagnosis; it may prove to be so in the understanding of disease. It is for this reason that the following, though brief and far from complete, is submitted.

Selye's Influence.

It has been known for many years that stress of any kind, for example, heat, cold, infection, trauma, that increased the activity of the autonomic nervous system also resulted in the release of adrenaline. Hans Selye developed the concept of the role of the adrenal cortex to explain disease in general and postulated that the adrenal cortex was concerned in some fundamental way in protecting the organism from stressful conditions. He set out to account for the dramatic results obtained by Hench in September, 1948, with cortisone in rheumatoid arthritis in terms of his hypothesis. Selye propounded the view that, whilst adrenaline afforded immediate protection against stress, the adrenal cortical hormones provided a more sustained effort, and his theory of the general adaptation syndrome with its stages of alarm, resistance and exhaustion is now history. Fierce controversy and terse, even bitter, criticism raged after his Heberden Lecture in 1950, and though many of Selye's views no longer find acceptance, it is pertinent to this discussion and will assist clarity to review his postulate in the light of what is now accepted or believed clinically and experimentally. The medical world owes a debt to Selye for the stimulus provided by his work, which has assisted in lifting the fog for the better understanding of disease, has aroused our intellectual curiosity and filled us with "an insatiable desire to see more".

In 1943 Selye gave desoxycorticosterone acetate and 1% saline solution to unilaterally nephrectomized rats and claimed to produce arthritic lesions similar to those found in rheumatoid arthritis and rheumatic disease. He affirmed that such diseases were attributable to an abnormal or excessive adaptive response of the adrenal cortex.

In 1946 he developed his theory further and claimed that as a result of the alarm reaction occasioned by stress in a living organism there was a discharge of adrenocorticotropic hormone (ACTH) which stimulated the adrenal cortex to overproduce its corticoids and so cause the diseases of maladaptation. His view was that a wide variety of medical disorders were due to an oversecretion of the mineralocorticoids, which are concerned with electrolyte metabolism, in contrast to the glucocorticoids, which are concerned with carbohydrate metabolism. In 1949, in view of the striking improvement brought about in rheumatoid arthritis and the rheumatic diseases with cortisone and ACTH by the Mayo group, Selye then suggested that ACTH produced the glucocorticoids only, and that the mineralocorticoids are produced by some other pituitary substance, which he called "factor x",[1] and that this "factor x" inhibits the production of the glucocorticoids. This should not be confused with the substance "x" which Hench has deemed to be the possible constituent of the body which can reverse rheumatoid arthritis. He and Kendall think that cortisone may well be this substance, so far as pregnancy is concerned, but the relationship between jaundice and rheumatoid arthritis still remains obscure. Added knowledge of cortisone has made the identity of substance "x" of Hench less important.

Though Selye was in error in assuming that rheumatic disease is caused by a disturbance of electrolyte metabolism due to an oversecretion of mineralocorticoids, it is only fair to him to say that his sensitizing experiments with desoxycorticosterone acetate have been confirmed by Harrison and others. However, Harrison observed that unilateral nephrectomy interfered with the adrenal arteries in such a way as to produce necrosis of the *zona fasciculata*, from which the glucocorticoids arise. Thus we have explained the value of the empirical therapy of arthritis with the glucocorticoid cortisone.

Theoretical Mechanism of the Adrenal Secretion of Steroid Hormones.

Some further preliminary observations might be made before proceeding to the main theme of this paper.

The present concept is that the adrenal cortex on stimulation by ACTH elaborates: (i) the group of steroid hormones, such as cortisone and compound F, that have the well-known therapeutic effects and influence carbohydrate, protein, fat and, to a much less extent, electrolyte metabolism; (ii) the group affecting electrolyte balance, such as compound S and desoxycorticosterone; (iii) the adrenal sex hormones, androgens, progesterone and œstrone; (iv) a residue that remains after separation of the crystalline compounds, known as the "amorphous fraction", and which also controls electrolyte metabolism.

The steroid hormones of the adrenal gland have in common a four ring carbon-hydrogen nucleus, and though many steroids of similar structure to cortisone have been tested, none other than compound F has been found to have its specificity in ameliorating the collagen and other diseases.

Hormones differ profoundly as therapeutic agents from other drugs, and their precise mode of action is still not understood. It is known that they influence the rate of metabolic reactions, but it is said (Engel) that they do not initiate them. It is considered likely that they may influence enzyme activity or affect permeability, and it is in this particular that the key may lie for their rationale in treatment.

Suggested Therapeutic Mechanisms.

Specificity for Some Unknown Factor Common to a Number of Diseases.

The first suggested therapeutic mechanism is that there is specificity for some unknown factor common to a number of diseases. This factor may be an enzyme, such as hyaluronidase, which is responsible for the spreading action on the ground substance in the interstitial spaces. It is thought that the adrenal steroids may prevent or arrest this abnormal enzymatic process in mesenchymal tissue, as, for example, in the collagen diseases.

Allergy.

The allergic theory postulates that the diseased state is due to hypersensitivity resulting from an abnormal response to an antigen that may be bacterial or endogenously produced, and that cortisone, for example, may protect the tissues, as in rheumatoid arthritis, from such an agent or antigen. Cortisone may limit the production of antigen and antibody, or it may protect the tissues from the products formed at the antigen-antibody or immune level.

It seems appropriate here to mention an exquisite piece of research work by a Finnish investigator named Järvinen. He produced evidence that there was no insufficiency of the adrenal cortex in bronchial asthma, one of the allergic group of diseases which respond to ACTH and cortisone. Patients during an attack of bronchial asthma were relieved by being placed in a low pressure chamber corresponding to an altitude of 4000 feet. The stress of such anoxæmia would impose a severe demand on the adrenal

[1] It is of interest to mention that at the Colston Research Society meeting at Bristol recently it was agreed that there might well prove to be two adrenocorticotropic hormones.

cortex with the output of cortical secretion. This investigator believes that it is adrenaline let loose by the stress which is the factor in relief of bronchial asthma and not so much the mineraloglucocorticoids.

Lessening of Capillary Permeability.

The concept of lessening of capillary permeability to explain the function of the adrenal cortex in response to stress or ACTH has received much prominence of late (Robson and Duthie, 1952). The test for resistance of the skin capillaries is claimed by these authors to be, in many instances, a more sensitive guide to adrenal cortical function than the eosinophile test. They found that whilst ACTH and the glucocorticoid cortisone increase capillary resistance along with clinical improvement, the mineralocorticoid deoxycortone acetate (DCA) causes a fall in capillary resistance and no favourable clinical response.

The thought that *nor*adrenaline, the vasoconstrictor secreted with adrenaline, in response to nonspecific stress, may be a factor in capillary resistance I leave to the physiologist, though, in passing, it should be mentioned that adrenaline stimulates the adrenal cortex in hypopituitarism.

The value of ACTH in thrombocytopenic purpura may be accounted for under this heading.

Damping Down of Cell Proliferation.

Damping down of cell proliferation would account for the transient action of ACTH and cortisone in malignant disease, Hodgkin's disease and leuchæmia. The antimitotic properties of X rays are their only biological actions established with certainty.

Selye's Adaptation Hypothesis.

Selye's adaptation hypothesis has been already dealt with.

Association of the Adrenal Cortex with Immunity.

The idea that the adrenal cortex is associated with immunity presupposes that the action of the cortical hormones in reducing lymphoid tissue increases the globulin level, and that the latter is associated with the carrying of antibodies, agglutinins and precipitins. On this basis certain antibodies are believed to be derived from lymphocytes and not from cells of the reticulo-endothelial system as has been hitherto believed.

Imbalance of Secretion of Adrenal Hormone.

The theory of imbalance of secretion of adrenal hormone hypothecates that there is a relative increase of the amorphous substance and desoxycorticosterone, which influence electrolyte metabolism, and that ACTH and cortisone supply the glucocorticoids to correct this feature. However, in rheumatoid arthritis the electrolyte metabolism is not altered significantly.

It is interesting to note in this connexion that ACTH was used at the Mayo Clinic in February, 1949, on a patient with rheumatoid arthritis. It was considered that if the adrenal cortex elaborated a product not normally present, stimulation of the cortex with ACTH would result in exacerbation of symptoms. The result, as we know, was great amelioration of the disease.

Physiological or Pharmacological Response.

Two reasons suggest that the response is physiological. Many patients with rheumatoid arthritis are relieved by a daily maintenance dose of less than 60 milligrammes of cortisone, which along with compound F has been found to be the dose excreted by a normal man; next, cortisone is delivered by secretion to the tissues more effectively for utilization than when it is given parenterally or orally, which suggests again a physiological process (Kendall).

The large doses required to secure reversion of disease suggest a pharmacological mechanism, though Dobriner discounts this, pointing out that the increase of hormone production in pregnancy from 50 to 100 times that of normal is accomplished without difficulty or harm to the patient.

Whatever the merits of these views may be, it would seem that an increased concentration in the blood of adrenal steroid is necessary to secure a clinical response and eosinopenia, and Kellgren and colleagues have recently put forward an explanation why the therapeutic response is so varied. The suggestion is that for any particular patient the amount of endogenously secreted adrenal steroid varies; if ACTH and cortisone are given when such concentration in the blood is high the output of adrenocorticotropic hormone from the pituitary is suppressed, the net result being no increase of adrenal hormone circulating in the blood and so no relief from symptoms.

A Substitution or Deficiency Basis for the Value of Therapy.

Against the theory that the value of therapy is on a substitution or deficiency basis: (*a*) there is no clear evidence of disease of the anterior part of the pituitary or adrenal gland in rheumatoid arthritis; (*b*) in Simmonds's disease rheumatoid arthritis is rare; (*c*) 20 milligrammes of cortisone are required to correct Addison's disease, whereas 100 milligrammes are required for rheumatoid arthritis; (*d*) ACTH produces similar effects to cortisone, showing that the adrenal cortex is capable of responding in a normal manner.

Action at the Periphery.

The concept described as action at the periphery depends largely on the work of Sayers (1950), who maintains that diseased tissue lacks a state of eucorticism and that the giving of ACTH and cortisone promotes this requirement. Though there is no evidence, so far, that adrenal steroid function is lacking in rheumatoid arthritis, it may be that the requirements of the corticoids by the tissues in this disease are high, or that such tissues are relatively insensitive and that the normal endogenous secretion requires the impetus of ACTH or cortisone. It seems a matter for speculation what the hypercorticism induced elsewhere may provide by way of side effects.

Suppression of Inflammation Arising from Various Causes.

Another view is that the mechanism is one of suppression of inflammation arising from various causes. By this view the tissue reaction to injury is lessened, but by no means the action of causal agents. It is apparent that this effect may ultimately be for the worse instead of for the better, since the steroid hormone may mask symptoms whilst the agent responsible is speeding the patient to disaster.

Discussion.

The foregoing observations furnish some idea of the perplexities that have confronted clinicians and research workers in their efforts to explain the mechanisms whereby ACTH and cortisone (*a*) are life-saving in some medical and surgical emergencies, (*b*) will revert a disabling disease within a few days, and (*c*) maintain relief in others. The eventual answer will probably be outside the realm of the many speculations that are here proffered. Some will say that it is the height of foolishness to probe for the site and manner of the actions of these agents in disease the mechanisms of which in turn we know so little. No apologies are needed for devoting so much time to Hans Selye. He would no doubt be prepared to admit the soft impeachment of having indulged in some peculiar lucubrations. His original concept has, however, cast a pebble into an ocean of controversy, of the ripple of which we see no end. With humble and naïve candour he says that the answer to the problem may prove as elusive as the comprehension of life itself, and he invites his audience to a synopsis of what he thinks he sees.

Two observations by Professor Brown, of Montreal and Philip Hench provide eloquent testimony of the dilemma of renowned thinkers.

The former draws the picture of disease in general as an iceberg with one-eighth above water—the observed specific reactions of the body to disease—and seven-eighths below

water, representing the general reaction of the body. ACTH, which stimulates adrenocortical production, melts away some of the under-water portion and causes the peaks to disappear below the surface. Hench, after drawing the simile of the "riddle wrapped in a mystery inside an enigma" mentioned in the opening paragraph of this paper, goes on to say that "they [ACTH and cortisone] do not put out the fire, kill germs, nor remove irritants, nor repair damage, but provide the patient with an asbestos suit in which he can walk in the furnace".

Summary.

1. Though inextricably mixed, physiological mechanisms have as far as possible been kept out of the discussion.

2. The word "treatment", let alone "cure", with ACTH and cortisone is still a misnomer when used in connexion with chronic or progressive disease.

3. Their mode of influence in ameliorating such states is not understood, and the dilemma of inquirers in this respect has been emphasized.

4. Their availability is a dire necessity for (*a*) clinical research, (*b*) life saving in some acute emergencies.

5. An attempt has been made to bring the concept of the general adaptation syndrome into perspective.

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IRUKANDJI STING TO NORTH QUEENSLAND BATHERS WITHOUT PRODUCTION OF WEALS BUT WITH SEVERE GENERAL SYMPTOMS.

By H. FLECKER,
Cairns, Queensland.

THE earliest reference to the subject of this paper in any medical literature is recorded in a letter by myself to THE MEDICAL JOURNAL OF AUSTRALIA, January 27, 1945, page 98.

> In the *Australian Journal of Science* (Volume V, Number 6, June, 1943), McNeill and Pope lay much stress on the fact that stings in the past inflicted on bathers in North Queensland have been almost invariably by Press and residents alike attributed to the Portuguese man-o'-war, sometimes known as bluebottle, a species of *Physalia*, one of the Siphonophores. This was certainly true in the Cairns district up to 1935, when the Registry of Injuries Caused by Plants and Animals was first established at Cairns as the result of a British Medical Association conference in that city, and an effort was made to study such problems on the spot.
>
> The injuries caused by the *Physalia* are quite easily and definitely recognized. The linear wheals, often multiple like streaks of lightning on the part afflicted, are unmistakable and the victim will direct attention at once to these. Like the familiar injuries seen frequently about Sydney, these are likewise found common amongst North Queensland bathers . . . .
>
> However, as soon as the registry was started, not only were *questionnaires* sent to all medical men practising in tropical Queensland, but detailed examinations were made of the numerous victims which took place every summer, the earliest being December 5 and the latest February 6, the vast majority being during the month of January. The cooperation of the Queensland Ambulance and Transport Brigade was particularly helpful in reporting these casualties and thus assisting in this inquiry.
>
> It was soon very evident that the great majority of the injuries were produced, certainly not by the *Physalia*, but by some other as yet unknown agent, and repeated efforts were made to discover what this agent was, and it was strongly suggested that some jelly fish, probably a very small one, was responsible . . . .
>
> The reporters in the early cases usually attributed the symptoms to the *Physalia*, but later on the ambulance staff and many residents were likewise convinced that some other agents were responsible, and great efforts were made to persuade witnesses and bystanders to look out for any jelly fish in the neighbourhood of the victim. The victim himself, of course, in all cases is much too ill to be concerned with such attention, and despite repeated efforts, no such medusa could ever be produced. However, with better dissemination of knowledge of these things amongst frequenters of the beach, there is no reason why such a search should not ultimately be successful, but so far the causal agent has not been satisfactorily demonstrated.

THE MEDICAL JOURNAL OF AUSTRALIA for April 21, 1945, page 417, published another letter containing the following.

> It appears then that about five jelly-fish at least are responsible for severe injuries to bathers, namely:
>
> (*a*) *Physalia pelagica*, producing lash-like weals and local symptoms mainly.
>
> (*b*) Another unknown organism producing similar symptoms, even fatal—perhaps the same as (*a*), but according to Mr. McNeill different.
>
> (*c*) Medusa in School of Tropical Medicine, Sydney, responsible for death of boy at Darwin. [This is the *Chiropsalmus quadrigatus* Haeckel, as determined by F. A. McNeill.]
>
> (*d*) A carybdeid medusa.
>
> (*e*) Unknown organism producing insignificant or unimportant local symptoms, but severe general symptoms so commonly met with in North Queensland waters.

It is with the group (*e*) alone that this article deals, and as apart from the above no reference prior to 1952 can be found in any medical or scientific literature, it is most desirable that a name should be adopted for reference purposes and also to facilitate the filing of articles on this subject, *urtica marina anœdematosa malibus gravibus generalisatis*. The name Irukandji has been chosen in the absence of knowledge of the identity of the offending object and of any distinctive single character amongst the symptoms. It is the name of an aboriginal tribe which formerly inhabited the coastal region between the Mowbray River to the north and the Trinity Inlet around Cairns to the south. Most of the recorded victims were stung in this region, and although the injury is not limited to this area, for some cases have been noted both north and east of this region, no more appropriate geographical name can be found at present.

Dr. R. V. Southcott, in THE MEDICAL JOURNAL OF AUSTRALIA for February 23, 1952, writes:

> Dr. N. S. Powys and myself saw about 100 more of such cases while we were medical officers attached to the "Beach Group" of the Australian Military and Naval Forces in that area. In about a dozen of our cases there was considerable local wealing without constitutional effects (which we designate Type B stingings), but in the remainder there were severe constitutional effects—nausea, vomiting, sweating, severe headache, extreme

and generalized pain, tachycardia, slight pyrexia—but with no wealing, and no more local effect than a patch of slight erythema at the site of the stinging, an area of, say, twelve centimetres by four centimetres (Type A stingings). In these Type A stingings there was a curious delay of from five to sixty minutes (usually twenty-five to thirty-five minutes) after the initial slight sting before the generalized effects started. We saw two cases with an irregularly irregular pulse. Like Dr. Flecker, we were unable to find the causative organism despite careful search. The common local jellyfish, *Pseudorhiza* sp., was found to be innocuous when applied to the skin . . . .

The Type A stingings referred to above are the Irukandji stings to which this article refers.

Geographical Range.

The most northerly reports are from Rocky Point, five miles south of Daintree River and seventy miles north of Cairns, and were sent in by Dr. H. S. Harper, who himself was a victim. Most likely the organism exists further north, but population higher up the coast is very scanty, giving little opportunity for securing records. The vast majority of the victims are stung along the foreshore of Cairns itself, and on the succession of beaches stretching northward from the mouth of the Barron River, where many visitors throng during the summer months and engage in bathing. To the east of Cairns is a peninsula with Cape Grafton at its north-eastern point. Some casualties have taken place on the north side of this peninsula, particularly at Brown Bay. No cases have been recorded from Green Island, a coral island twelve miles from Cairns, despite the fact that it is very well patronized by bathers. Indeed, except from the mainland, no cases have been recorded from any of the numerous islands or from any part of the nearby Great Barrier Reef. Doubtless after this report has been published many cases will be noted south of Cape Grafton and the southern limit of the geographical range ascertained.

Beach Conditions.

The injuries usually take place in quite shallow water up to about four feet in depth, and victims may be either standing on the sandy bottom or actually swimming, but so far there is no record of any sting in much deeper water. The weather may be fine and the water calm, as is usual when large numbers of people, that is, children of all ages and adults, are bathing, but it may also be quite rough and stormy.

Earliest Records.

The first record received by the registry was on a *questionnaire* form, very imperfectly filled in, from the Cairns Base Hospital, dated February 2, 1936. The injury was to a female, aged twenty-six years, and was referred to as being caused by the "Portuguese man-o'-war", as were almost all those occurring about that time, the date of the incident being December 29, 1935. The name of the locality was not given, and the only relevant notes were: "Abdominal pain, pain in legs, vomiting, severe shock." The site of the part of the body stung is not indicated, nor is there any information of the presence or absence of weals, but it is evident that this is an example of the Irukandji sting. Apparently this is the earliest case recorded, but three other very imperfectly described cases from the same source were reported, some associated with very severe general symptoms.

Seasonal Influences.

As the condition became more clearly defined, with each passing summer more cases were examined, and it was found that practically all victims were stung during the months of December and January; very rarely were victims stung in February, and the maximum incidence was during the last and first fortnights in each year, corresponding to the peak of the holiday season, the period when the maximum number of bathers indulge in the opportunities for a swim. The earliest casualty occurred on December 5 and the latest on February 6.

During the first summer in which observations were made, notes were made of six victims stung between December 29, 1935, and February 6, 1936. In the next summer nine were recorded between December 27, 1936, and January 27, 1937. Only three were recorded between December 3, 1937, and January 31, 1938, but a large crop of at least 15 were seen from December 26, 1939, to February 3, 1940. Of course these do not represent the actual prevalence, even approximately, as most cases were unrecorded, but it indicates the annual incidence; perhaps the cases are much more common in certain summers than in others. Seven cases in a single day were reported on January 29, 1940, but most likely many more such casualties on a single day take place upon other occasions. After all, the number of patients recorded depends very much upon the interest and enthusiasm of medical and other attendants. Sometimes weeks may pass during these summer months without record of any cases at all, and in this time there may be actually no victims.

Southcott reports having seen 100 victims during the 1943-1944 summer. Whether the cases were more prevalent that season than previously is questionable; more likely the peculiar conditions under which numerous army and naval personnel operated—American as well as Australian—would account for the greatly increased incidence, medical and other personnel associated with the activities of forces training for beach warfare being far more numerous. As previously stated, the number of victims recorded depends much on the interest and enthusiasm of medical and other attendants.

Cause of Injury.

The cause of the injury is very much a mystery. One victim stated that he saw one long thread of slimy greenish jelly-like appearance, of the thickness of an ordinary piece of string and about two feet long. Although no weal was produced, there are indications that this particular injury may be different from the Irukandji.

In an attempt to discover the culprit, five substations of the Cairns Surf Life Saving Club distributed on different beaches were supplied with "D" nets, similar to those employed for catching prawns and other baits, with requests to scour the neighbourhood immediately after victims have been stung, but so far this has produced no results. It is hoped later in the year to seek a conference between representatives of the Queensland Ambulance Transport Brigade, the Cairns Surf Life Saving Club mentioned above, the various beach progress associations and others willing to help in joining in the search for the agent responsible.

Previous Attacks.

In the great majority of cases there is no history of any previous attacks. Occasionally one or more previous attacks, probably by *Physalia*, are mentioned, but this is quite unusual and in any case is unimportant.

Site and Character of Local Sting.

The sting may, of course, occur on any part of the body below the surface of the water. The puncture, if any, is often quite invisible, and even the victim himself is unable to see any local mark where he may feel the sting. In any case it is always small and very insignificant, comparable perhaps to a flea bite. Only occasionally are there such notes as "red streaks at the site of the sting" or "little white spots slightly larger than a pin's head". Southcott states that there is "no more local effect than a patch of slight erythema at the site of the stinging, an area of, say, twelve centimetres by four centimetres".

Local Pain.

Generally the pain at the site of attack feels like the sting of a wasp, causing the victim to dash hurriedly and at once for the shore. One victim described a sensation like the prick of a hot needle through the woollen bathers on to the scrotum. Sometimes the pain is slight, one victim declaring that he felt the sting but there was no pain.

Usually the victim cries out that he has been stung, but occasionally local pain is completely absent and the victim is unaware of having been stung at all or of where he has suffered injury.

Latent Period.

The time which elapses between the moment of being stung and the onset of severe symptoms varies considerably. It may be a couple of minutes, perhaps five, ten, twenty or more, generally sufficient for the victim to race ashore, but sometimes very much longer. Dr. Southcott estimates "a curious delay of from five to sixty minutes (usually twenty-five to thirty-five minutes) after the initial slight sting before the generalized effects started".

Delayed Onset.

Sometimes the general symptoms are very much delayed, especially amongst those who do not experience any local sting or are unaware of having been stung at all. One woman while bathing at Ellis Beach did not feel any sting, but complained of severe pain behind the knee ten minutes after coming out of the water, with pains across the back and other severe symptoms rendering her too ill to stand. Another little girl, aged eleven and a half years, although she felt no sting and saw no offensive object in the water at Brown Bay, proceeded to dress an hour and a half after leaving the sea. Pain commenced eighty minutes after her emergence from the water; it started in both legs whilst she was watching some captive crocodiles. After dressing was completed the pain was so severe that she was unable to stand. Another adult victim was mildly stung at Trinity Beach, but not until many hours later, after a drive home to Atherton, seventy miles distant, did severe general symptoms commence.

General Symptoms.

The severe general symptoms are those of shock, resulting in collapse, severe generalized muscular pains, more particularly of the abdominal wall and thoracic cage, vomiting *et cetera.*

Shock.

Often immediately after the victim reaches the beach, rarely before and sometimes only a little afterwards, the most prominent feature is shock, resulting in complete collapse; ambulance aid is immediately sought, but it does not arrive for about half an hour or so, depending on the location of the beach.

Generalized Pain.

Agonizing pain is frequent; it may be generalized throughout the body, and is described perhaps as being most intense in some particular region, for instance, down the back, over the muscles of the abdominal wall or those of the chest, or down the lower limbs. It appears to be cramp-like in nature, causing individuals to writhe with pain. Sometimes patients describe it as moving from one region to another, as though afflicting different groups of muscles in turn, but its location has no relation apparently to the site of the original sting. Even hypodermic injections do not appear to relieve the distress, at least for the time being, and these are usually not given until the patient has reached hospital or has been examined by his medical attendant. More recently, however, ambulance attendants are equipped with a "Trilene" outfit, so that relief is much more prompt. The pain is certainly the most distressing feature of the incident.

Vomiting.

Vomiting is a most prominent feature and takes place early, accompanied by painful and violent retching. It is preceded by nausea, which is occasionally present without vomiting. Medicaments such as aspirin which may be administered may be promptly returned.

Sweating.

Profuse sweating accompanies the violent cramps and muscular pains. The victim by this time is quite helpless and unable to stand or dress.

Headache.

Headache is not a prominent feature, for most victims do not mention this. However, Dr. Southcott lists severe headache as one of the symptoms.

Temperature, Pulse and Respiration.

High temperatures have not been observed. The pulse rates recorded vary between 72 and 102 per minute, with one count of 126 per minute. Respiration rates recorded are between 16 and 31 per minute. Southcott lists slight pyrexia and tachycardia as symptoms.

Course.

After a longer or shorter period of acute discomfort the victim slowly recovers, and usually by the next day, apart from some evanescent soreness, has returned to normal. No fatal cases have yet been observed.

Summary.

1. A description is given of Irukandji sting, caused by an unknown marine object, probably a small jellyfish.

2. It has been geographically recorded so far only between Rocky Point, south of the Daintree River, and Brown Bay in Trinity Bay, but probably extends both further north and further south respectively of these points.

3. Victims are afflicted only during the summer season, the earliest recorded case being on December 6 and the latest on February 5.

4. A local, small, insignificant puncture is present, accompanied by a sharp sting like that of a wasp, but this is not invariable. The absence of weals is characteristic.

5. There is a latent period from a couple of minutes to an hour or so, but occasionally a much longer delay occurs before the onset of severe symptoms.

6. Severe symptoms consist of shock with collapse, severe cramp-like pains in various groups of muscles (such as those of the back, abdominal wall, chest and limbs) not related to the site of the sting, nausea, painful retching and vomiting requiring hypodermic injections of morphine or administration of "Trilene" for relief.

7. Certain minor symptoms occur of much less importance.

Reports of Cases.

TWO CASES OF COMPLETE TRANSPOSITION OF THE GREAT VESSELS OF THE HEART.

By MICHAEL ELYAN,
Pædiatrician, Townsville Hospital,
AND
F. C. RUFFLE,
Resident Medical Officer, Townsville Hospital, Townsville, Queensland.

GIBSON AND CLIFFORD described nine cases of complete transposition of the great vessels of the heart among 105 children with congenital heart disease. Complete transposition occurred in 49 of Abbott's series of 1000 patients.

There are several possible types of faulty arrangement of the great vessels.

1. The aorta may straddle both ventricles, and usually there are accompanying defects of cardiac septa and the pulmonary artery.

2. Both the aorta and the pulmonary artery may rise from the right ventricle; this is incompatible with life beyond a few weeks or months.

3. In true transposition the aorta rises from the right ventricle and the pulmonary artery from the left ventricle;

therefore, blood is carried from the right side of the heart through the systemic circulation, and returns to the right side. The pulmonary artery transports blood from the left side of the heart to the lungs and the blood returns to the left side.

The clinical manifestations are as follows. Cyanosis occurs shortly after birth. If the *ductus arteriosus* is patent, cyanosis is less intense in the lower extremities than in the rest of the body, because aerated blood entering the aorta through the ductus is distributed chiefly to the lower half of the body (Taussig). Clubbing of the fingers and dyspnœa are present. Murmurs may be present, but not sufficiently typical in quality or location to be of diagnostic value.

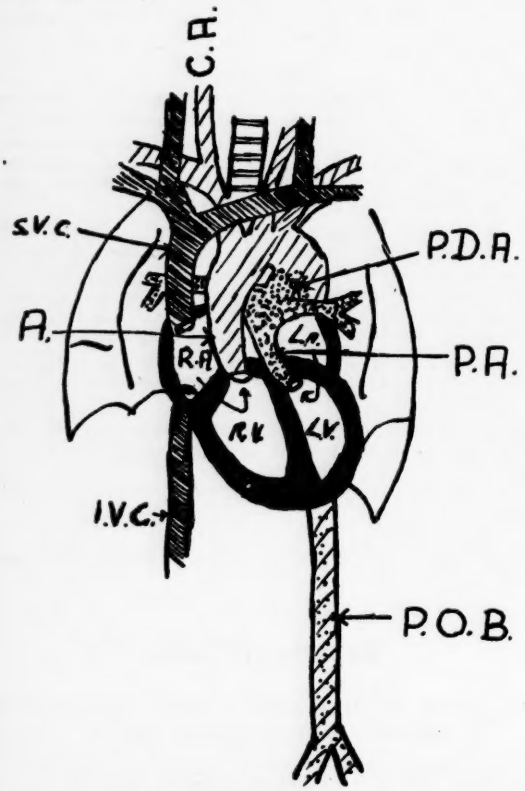

FIGURE I.

Case II. C.A., carotid artery; P.D.A., patent *ductus arteriosus*; P.A., pulmonary artery; P.O.B., partly oxygenated blood to the lower extremities; I.V.C., inferior *vena cava*; A., aorta; S.V.C., superior *vena cava*; R.A., right auricle; R.V., right ventricle; L.A., left auricle; L.V., left ventricle; hatched areas, venous blood; dotted areas, oxygenated blood.

The prognosis is poor. The majority of patients do not survive the age of infancy, unless there is adequate admixture of blood through a patent *foramen ovale*, ventricular septum or *ductus arteriosus*. In such instances patients may reach adulthood.

Case I.

Baby T., aged forty-one days, was admitted to this hospital when it was eight days old. An accompanying letter stated that the baby had been cyanosed since birth and that the degree of cyanosis seemed to be increasing. Since the parents could not speak English, it was impossible to ascertain the nature of labour. The baby was breast fed and took its food fairly well, but was often considerably distressed afterwards.

On examination the baby was seen to be cyanosed, the cyanosis being more pronounced in the head and upper extremities than in the trunk and lower extremities. The baby was in great respiratory distress, the rate being over 140 per minute, and had a temperature of 100·2° F. There was slight finger clubbing, but apart from these there were no abnormal physical signs. A provisional diagnosis was made of congenital transposition of the great vessels, or birth injury.

A number of investigations were carried out. The hæmoglobin value was 19·2 grammes *per centum*, the mean cell diameter was 7·3μ, and a blood film revealed no abnormality. An X-ray examination of the chest revealed no abnormality in the lung parenchyma. The heart appeared normal.

The baby was given oxygen continuously, and with this treatment the cyanosis diminished slightly. During its stay in hospital the baby had periodic attacks of acute respiratory distress, these being particularly noticeable after feeding. The baby died in such an attack twenty-seven days after admission to hospital.

At the post-mortem examination a complete transposition of the great vessels was found, with a patent *ductus arteriosus*, but no other abnormalities of the heart itself.

Case II.

Baby K., aged two months, was admitted to this hospital twelve hours after the death of Baby T. An accompanying letter stated that the baby had been cyanosed since birth, that it was starting to lose weight, and that it was not taking its food properly. There was no history of a difficult labour, and the baby was breast fed.

On examination the baby was cyanosed, the cyanosis being more pronounced in the head and upper extremities than in the trunk and lower extremities. The baby's respirations numbered 100 per minute; its temperature was normal. A soft systolic murmur was heard to the left of the sternum in the fourth left intercostal space. Apart from these, there were no other abnormal physical signs.

A provisional diagnosis of congenital transposition of the great vessels was made.

An X-ray examination of the chest revealed no abnormality.

The baby was given oxygen continuously, but its condition did not improve and it died twelve hours later.

Post mortem complete transposition of the great vessels was found, with a patent *ductus arteriosus* and a semi-patent valve in the interauricular septum.

Summary.

Two cases of complete transposition of the great vessels of the heart, confirmed by post-mortem examination, are reported. The cases occurred within one month of each other.

References.

Abbott, M. E. (1936), "Atlas of Congenital Cardiac Disease", "New York American Heart Annual".

Gibson, S., and Clifford, W. M. (1938), "Congenital Heart Disease. A Clinical and Postmortem Study of 105 Cases", *American Journal of Diseases of Children*, Volume LV, page 761.

Reviews.

CLINICAL NEUROLOGY.

IN preparing "A Textbook of Clinical Neurology" Nielsen was clearly aware of his difficulties, and in the preface he outlined the method he would follow.[1] "Since the birth of neurology as a specialty almost exactly a century ago the subject has grown beyond the capacity of any one human mind. . . . The book aims to present the subject of clinical neurology working from the simple to the complex (from below upwards anatomically) in so concise and clear-cut a manner and in sufficiently small volume that it may be used as a text of the subject during the time allotted to neurology in a general medical course. . . . To facilitate comprehension without commitment to memory, intimate correlation of symptomatology with the basic subjects of anatomy, physiology, pathology and pharmacology has been stressed."

[1] "A Textbook of Clinical Neurology", by J. M. Nielsen, B.S., M.D., F.A.C.P.; Third Edition; 1951. New York: Paul B. Hoeber, Incorporated. 10½" × 7½", pp. 724, with 212 illustrations. Price: $10.00.

It may be said that the author has succeeded to some extent in his high aim of facilitating comprehension without commitment to memory, yet contrary to his expressed statement, this is partly at the expense of the basic sciences. However, this is permissible in attaining the desired end. Moreover, the presentation lacks balance, revealing clearly the interests of the writer. In a text of nearly 700 pages of large print, herniation of a pulp nucleus has little more than half a page devoted to it; subacute combined degeneration of the cord is dismissed in three pages, and none of its fascination is brought out. Intracranial aneurysms have less than two pages. Included is the statement: "The posterior group are about the posterior communicating and the posterior cerebral arteries. This latter group, when they give symptoms, indicate the site by affecting the IX, X and XI cranial nerves". On the contrary, the inflammations and intoxications cover 120 pages. It is readable, but some of the space devoted to rarer conditions might well have been devoted to common conditions which are given scant notice elsewhere. The new chatper on epilepsy is very short and bases a clinical presentation upon the work of one school of electroencephalographers. Thus *petit mal* is described as being of three types: momentary loss of consciousness with possibly chewing and swallowing movements (thus losing the focal implications of the latter), akinetic epilepsy and myoclonus epilepsy. Idiopathic epilepsy is defined as that in which no gross lesion of the nervous system can be established during life by all usual methods of examination. Yet as its causes are given asphyxia with subsequent cortical or subcortical damage, direct trauma to the brain, infections and epiloia.

The use of eponyms is a matter of personal preference: yet their usage in the text advances reasons against them. Thus many pages are devoted to brain-stem syndromes, because proper names have been added—syndromes which the student very rarely, if ever, sees, and if he did could work out satisfactorily from his anatomical knowledge. (Wisely he is advised elsewhere not to be above reference to a text-book of anatomy.) Most neurologists readily understand what is meant by attention hemianopia, but would be perplexed as to the meaning of Riddoch's syndrome. Again, imperception of hemiplegia conveys a meaning, Babinski's anosognosia would puzzle many. Nor is the usage always correct. Jacksonian seizures are referred to as "involuntary clonic contractions of the musculature of one side of the body (limbs and face) without loss of consciousness". The term Guillain-Barré syndrome has been given wide significance which the original authors did not describe; on the the other hand, the use of the term Landry's paralysis is rightly condemned. Eponyms tend to perpetuate the names of the describers of small details; on the other hand those who are responsible for major discoveries and advances remain unnamed. (The matter is certainly a difficult one: perhaps it is reasonable to retain the names of the great, and expedient to retain those having a well-established meaning.)

The author's attempt to make an unusual classification has obviously given him much trouble. To quote a minor instance, mononeuritis due to extension of inflammation from neighbouring structures includes such causes as involvement by malignant tumours and chilling of a local area. The unwieldy term *mononeuritis multiplex* has been created.

Treatment is not well discussed. Of subacute combined degeneration all that is said is: "The treatment is, of course, that of the underlying disease. In the subacute combined degeneration of macrocytic anæmia, folic acid may restore the blood picture but not the spinal cord and nerves. In a few instances cobalt containing vitamin B_{12} has done away with paræsthesiæ, but it is too early to be dogmatic about such effects. At present it seems that folic acid stimulates maturation of blood cells in the bone marrow, while vitamin B_{12} acts on cellular enzyme systems." In Ménière's syndrome it is said that if desensitization with histamine diphosphate fails "it is justifiable to subject the patient to surgical exploration of the cerebellopontine angle in the hope of finding a vascular anomaly or other removable cause". Phenobarbital is considered to be the best drug for major epilepsy. If the student gained much from the description of trigeminal neuralgia, the sufferer from true *tic douloureux* would endure much investigation before treatment by injection or surgery was undertaken. There are some significant misprints: streptomycin 2 mg. daily is condemned; "with dosage reduced to 1 Gm per day most of the complications can be avoided".

Some of the material is very good. Clinical cerebral localization is presented in such a manner as to stimulate the student's interest. The description of the types of involuntary movements is clear. On the whole the text is eminently readable and few, at a later and more critical stage of development than that of the usual student, would not benefit from reading it. The student if he had time could well read part, but in conjunction with other books. The index, following "no rule except that of ready reference", is excellent. The production of the book, of standard American type, is excellent.

EYE, EAR, NOSE AND THROAT DISEASES.

THE section on the ear, nose and throat in "The 1951 Year Book of the Eye, Ear, Nose and Throat" has a new editor, John R. Lindsay, who has taken over from the previous editor, Samuel J. Crowe, and his collaborator, Elmer W. Hagens, and Derrick Vail continues to edit the section on the eye, in which he has arranged his material in a manner substantially the same as that in the previous year book.[1] Chapters are devoted to the eyelids and lachrymal apparatus, the orbit and exophthalmos, the conjunctiva, the cornea, the lens and cataract, the iris, ciliary body and choroid, the optic nerve, the retina, neurology and visual fields, glaucoma, refraction and motility, surgery, therapy, and miscellaneous subjects. Many subjects are touched on; amongst those that seem to have attracted most attention during the year are retrolental fibroplasia and treatment with ACTH and cortisone. The editor is sparing in his comments. A wide range of journals is covered, and the physician and the neurologist as well as the ophthalmologist should find a good deal to interest them. The section on the ear has chapters on hearing and hearing tests, vertigo, deafness and Ménière's disease, tubal function and *otitis media*, otosclerosis and fenestration, and miscellaneous subjects. The section on the nose and throat has chapters on the nose and sinuses, the oro-pharynx and naso-pharynx, plastic procedures, the larynx and hypopharynx, the trachea, bronchi and œsophagus, allergy, and miscellaneous subjects. Ménière's disease and particularly its surgical management continue to attract attention, as do otosclerosis and the fenestration operation. The pros and cons of tonsillectomy still seem to provide material for discussion, as does carcinoma of the larynx. Tracheotomy for patients with bulbar poliomyelitis has gained in favour, but has its opponents. Indications for its use have been found in a number of other conditions. Although much of the material in the sections on the ear, nose and throat is of primarily specialist interest, it will repay perusal by the general practitioner, the physician and the pædiatrician. The production of the volume is in accordance with the high standard of the whole series.

A PIONEER OBSTETRIC NURSE.

IT is not yet fully recognized that the profession of nursing has behind it an enviable tradition of devoted service and noble achievement; and we are apt to overlook the fact that for the last eighty-four years Australian nurses have been building up a fine record of which the country has every reason to be proud. So much has been written about the history of nursing in the last few years that training schools might with advantage impart some of this knowledge to their young neophytes; it should give them a higher sense of their vocation to be made aware of the fine traditions established and maintained by their worthy predecessors.

A valuable addition to the literature of this subject appears in the form of a small book entitled "Alice and the Stork", written by Dr. Egbert Morland, sometime editor of *The Lancet*.[2] He gives an interesting account of the life and work of Miss Alice Gregory (1867-1944) whose unremitting efforts to introduce modern methods to obstetric nursing coincide with the gradual rise in the status of the midwife in England. The whole story serves to emphasize the value of early home training, a liberal education, and the need for a high standard of efficiency in any special department of medical care which the young nurse decides to adopt as her vocation.

[1] "The 1951 Year Book of the Eye, Ear, Nose and Throat (October, 1950-September, 1951); The Eye, edited by D. Vail, M.D., D.Oph. (Oxon.), F.A.C.S.; The Ear, Nose and Throat, edited by J. R. Lindsay, M.D.; 1952. Chicago: The Year Book Publishers, Incorporated. 7¾" × 5¼", pp. 456, with 131 illustrations. Price: $5.50.

[2] "Alice and the Stork: Or the Rise in the Status of the Midwife as Exemplified in the Life of Alice Gregory, 1867-1944", by Egbert Morland; 1951. London: Hodder and Stoughton, Limited. 8" × 5¼", pp. 88, with 14 illustrations. Price: 7s. 6d.

Miss Alice Gregory was a daughter of the Dean of Saint Paul's Cathedral, London, and the yearnings of a social conscience fired her with an ambition to devote herself to the women of rural England as an obstetric nurse. After completing a perfunctory course of training, she left London and settled down to practise in a country district of Somerset, where she remained for several years. Her attitude to the new experience is best revealed in her letter to a friend:

> If I could but make you see, for one moment, all the satisfactions of a midwife's life as they have unrolled themselves to me during the last eight years! The independent, open-air, vigorous life, in close touch with the Eternal Verities; the keen, scented, early morning air, with the lark going up under your feet, as you hurry over the fields to some outlying cottage; the fragrance of the stocks and white pinks as you push the little gate, just visible in the coming dawn; the sick woman's note of thankfulness, "Oh, nurse, I was so frightened, but I don't mind anything now you've come"; the calling forth of your whole faculties in the one effort to do all of your duty.

This book is a fine tribute to one of the pioneers of modern obstetric nursing, who devoted the greater part of a long life to working for higher standards of education and training for the obstetric nurse, and for the universal adoption of improved measures for the reduction of maternal and infant morbidity and mortality.

There are several interesting illustrations, one of which shows the aged Sister Gregory surveying the ruins of her own obstetric hospital after the Germans had reduced part of it to a heap of rubble.

Notes on Books, Current Journals and New Appliances.

THE SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY.

THE Sixth International Congress of Radiology was held in London in 1950.[1] There has now been issued a small pamphlet on the organization of the Congress. It describes the preparations made for the Congress and the Congress itself; no account is given of papers read. The arrangements made for the proper functioning of the Congress are set out, and the entertainments and so on are enumerated. No less than 3093 members were registered, and 55 countries were represented. The cost of the Congress was £28,750. At the closing ceremony the president stated that the closing of one congress was merely the opening of the door which led to the next. It is stated that the fundamental problems facing the organizers of all congresses are much the same, and that lessons learned at one meeting can be useful in the running of another. This pamphlet is published in order to be of help in this direction.

DORLAND'S MEDICAL DICTIONARY.

THE twenty-second edition of the American Illustrated Medical Dictionary, commonly known as Dorland's Medical Dictionary, has been published.[2] This work, which needs no introduction to the medical profession, has been appearing regularly since the year 1900. The author's aim is "to give its readers the most complete coverage possible of the fast-growing medical vocabulary". Dr. Dorland is well qualified to do this, but he has the help of an editorial board. On this board are R. M. Hewitt, of the section on publications of the Mayo Clinic, E. C. L. Miller, a directing librarian emeritus, and A. H. Sanford, an emeritus professor of clinical pathology. Further contributors have been L. W. Daley, Associate Professor of Clinical Studies in the University of Pennsylvania, and Austin Smith, editor of *The Journal of the American Medical Association*. In this edition a new type has been used and many illustrations and new terms have been added. The word to be defined is printed in heavy type, and for the rest a clear type face is used. The derivation of words is given, and when words come from the Greek, the word of origin is printed in Greek characters. This is most satisfactory. An important feature is an introductory article on the fundamentals of medical etymology. The student of medical terms would be well advised to study this. At the back of the book is an extremely useful table extending over several pages, in which modern drugs and their dosage are set out. The headings of this table include the type of agent, the drug or preparation, the average adult dose, and dosage forms. Some of the groupings in the body of the book are useful. For example, culture media are described in alphabetical order, and methods used in the laboratory extend over some pages. Stains and staining methods cover many pages and appear to give all the information that may be needed. The list of tests is formidable and covers some forty odd pages. The colour plates are well produced. In short, this is the kind of book that is indispensable to any student of medicine.

[1] "The Organization of the Sixth International Congress of Radiology: London, 1950", published under the authority of the British Executive Committee; 1951. London: H. K. Lewis and Company, Limited. 9" × 6", pp. 44. Price: 3s. 6d.

[2] "The American Illustrated Medical Dictionary: A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology and Medical Biography with their Pronunciation, Derivation and Definition", by W. A. Newman Dorland, A.M., M.D., F.A.C.S.; Twenty-Second Edition; 1951. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10" × 7", pp. 1762, with 720 illustrations. Price: £5 9s. 3d.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Histopathological Technic: Including a Discussion of Botanical Microtechnic", by Aram A. Krajian, Sc.D., and R. B. H. Gradwohl, M.D.; Second Edition; 1952. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9" × 6", pp. 362, with 131 text figures and seven colour plates. Price: £3 11s.

For medical students, technicians, research workers and laboratory directors.

"Bone Tumors", by Louis Lichtenstein, M.D.; 1952. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10" × 7", pp. 316, with 155 illustrations. Price: £5 10s. 3d.

Describes the clinical features, pathology, treatment and prognosis of each type of bone tumour.

"The 1951 Year Book of Dermatology and Syphilology (December, 1950-November, 1951)", edited by Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D.; 1952. Chicago: The Year Book Publishers, Incorporated. 8" × 5½", pp. 476, with 61 illustrations. Price: $5.50.

One of the Practical Medicine Series of Year Books.

"Advances in Pediatrics", edited by S. Z. Levine, with associate editors Allan M. Butler, Margaret Dann, L. Emmett Holt, junior, and A. Ashley Weech; Volume V; 1952. Chicago: The Year Book Publishers, Incorporated. 9" × 6", pp. 274, with 21 plates and many text figures. Price: $7.00.

Contains articles on the treatment of bacterial meningitis, the nephrotic syndrome in children, vitamin *K* deficiency and hæmorrhagic disease of the newborn, angiocardiography in children, iron metabolism in children and BCG vaccination.

"James Lind: Founder of Nautical Medicine", by Louis H. Roddis; 1951. London: William Heinemann (Medical Books), Limited. 8½" × 6", pp. 188, with eight illustrations. Price: 21s.

The story of an eighteenth century naval surgeon and his place in the conquest of scurvy.

"Atlas of Human Anatomy", by Franz Frohse, Max Brödel, and Leon Schlossberg, with an explanatory text by Jesse Feiring Williams, M.D.; New Edition; 1952. London: George Allen and Unwin, Limited. 8½" × 5½", pp. 90, with 67 illustrations, many in colour, and eight text figures. Price: 16s.

A brief pocket-sized atlas for the use of both the medical practitioner and the layman.

"The Rhesus Factor", by G. Fulton Roberts, M.A., M.D. (Cantab.); Third Edition; 1952. London: William Heinemann (Medical Books), Limited. 7½" × 5", pp. 98. Price: 5s.

A third edition of the booklet reviewed in this journal on December 3, 1949.

The Medical Journal of Australia

SATURDAY, JULY 19, 1952.

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INTERNATIONAL MEDICINE, AUSTRALIA AND THE FUTURE.

IT is a commonplace to say that the world is becoming smaller as the years pass. For this wireless broadcasting and air travel are of course mainly responsible. The nations have learned and are learning more about one another, and the aspirations and ideals of one group of peoples are being exposed to the searching scrutiny and study of others. Scrutiny may lead to approval and to adoption of ways of life or of points of view perhaps in a modified form suited to a new environment. In this regard the two world wars opened the eyes of many nations either because of troops sent from them for military service in other countries or because of armies which came from abroad to fight as allies within their borders. There is no reason to suppose that the state of affairs will remain as it is at present. On the contrary, conditions of life vary so much in different places that fresh problems are bound to arise and adjustments will have to be made. The nation which is thoroughly alive to the situation and which has its own house in order will be able to make the greatest contribution to the common good and will be able to preserve what it has of cherished value. Australia is peculiarly placed from a geographical point of view. Her closeness to the nations of southern and south-eastern Asia and her distance from other countries which have her way of life make it inevitable that she will have to deal some day, and perhaps soon, with problems which they will present to her.

The general economy of a nation is inseparable from its health, and the more "enlightened" a nation, the more it will strive to secure the mental and physical welfare of its inhabitants. It is a little more than one hundred years since any international cooperation in the matter of health was attempted. What has been done in the international sphere since then has been reviewed by Neville M. Goodman in an attractive volume entitled "International Health Organizations and their Work".[1] This volume should receive the careful attention particularly of all who are active in the world of medical politics, those who have been elected to the Federal or Branch Councils in Australia. Goodman draws attention to a statement in the preamble to the constitution of the World Health Organization that: "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition." Further: "Governments have a responsibility for the health of their peoples which can be fulfilled only by the provision of adequate health and social measures." International health activities are described as "any or all of those activities for the prevention, diagnosis or treatment of disease which require the combined consideration and effort of more than one country". The first international effort at health organization was made in 1851. Goodman writes that the idea of an international sanitary conference between governments interested in reducing quarantines and in keeping out cholera and other epidemics was becoming more and more insistent. On July 23, 1851, the representatives of twelve States met in Paris. The States represented were Austria, the Two Sicilies, Spain, the Papal States, France, Great Britain, Greece, Portugal, Russia, Sardinia, Tuscany and Turkey. The official objective of the conference was "to regulate in a uniform way the quarantines and lazarettos of the Mediterranean". It is noteworthy that each State was represented by one medical man and one diplomatist, the latter being drawn from the consular services "in view of the commercial interests involved". The gaps in the medical knowledge of the matters concerned were of course enormous, and it is not surprising that the medical members could not come to any agreement. Even had they been able to do so, it would have been of no use, for "the diplomats had very definite instructions and were unable to recommend unanimously either the abolition or the retention of quarantines, whatever the medical opinion might have been". Thus the conference proved abortive. Goodman thinks, however, that in the light of subsequent events and later discoveries this was perhaps all to the good. The conference had drawn up a series of regulations, but though the convention and regulations were signed by all the powers at the conference, subject to reserves and to ratification, ratification was carried out by only France, Portugal and Sardinia. Portugal and Sardinia withdrew in 1865. Goodman points out that in spite of apparent failure the conference of 1851 did achieve certain objectives which included the laying down of some important principles. Many conferences were subsequently held, but it was not until the twelfth conference took place in 1907 that a permanent world-wide international health body was created with headquarters at Paris—*L'office internationale d'hygiène publique*. At a conference held at Paris in 1926 a convention revised and enlarged from one adopted in 1912 was agreed upon and is still the basic convention governing quarantine by sea and land. A summary of the general provisions of this convention by F. McCallum

[1] "International Health Organizations and Their Work", by Neville M. Goodman, M.A., M.D. (Camb.), F.R.C.P. (London), D.P.H. (London Univ.), with a foreword by Sir W. Wilson Jameson, G.B.E., K.C.B., M.D., F.R.C.P., D.P.H.; 1952. London: J. and A. Churchill, Limited 9½" × 6¼", pp 338, with 53 illustrations. Price: 35s.

was published in 1935 by the Commonwealth of Australia in "Service Publication" Number 40. Goodman observes that the second half of the nineteenth century and the first two decades of the twentieth constitute the first phase of collaboration between nations in the field of health. Then came the Health Organization of the League of Nations, which may be said to have started on its useful career in 1921, when Dr. L. Rajchman was appointed medical director. The work of this body cannot be reviewed here; many of its activities have been discussed at various times in its pages during the life of this journal. In 1946 the functions of the Health Organization were transferred to the United Nations. The health work of the United Nations Relief and Rehabilitation Administration (UNRRA) and of the World Health Organization can only be mentioned in this short outline—what they have done and are doing is known to most medical practitioners.

Goodman sets out under seven headings the types of international health work which are needed: (i) The control of epidemics and communicable diseases affecting more than one country, including the exchange of information about epidemic disease, quarantine and so on. (ii) The international exchange of medical and health information and experience. (iii) The international standardization of vital statistics, biological preparations *et cetera*. (iv) Combined research on specific problems common to many countries. (v) Help to backward countries, including epidemic control, administrative medical planning and training of health staff. (vi) Advice to governments and health authorities on health questions with a national bearing. (vii) Medical aspects of the international control of drugs. There can be no argument about the importance of these things; such questions as food supplies and housing are included among the items mentioned. They are all of interest to the whole medical profession, but they are the care of governments and of organizations formed and fostered by them. Australia has always taken an active part in what has been done, and the Government of the Commonwealth must be trusted to make sure that Australia will take her proper place and make an adequate contribution to the solution of any international problems of the future.

There is another side of international medical activity which is non-governmental and which is the concern of the medical profession considered as a practising entity and not as dominated by governments or by bodies created or controlled by them. The same considerations about the future must be borne in mind in regard to this aspect. The World Medical Association is the body to which attention and assistance must be given. There is a section of the medical profession in this country which looks askance at the World Medical Association, partly because no immediate advantage can be expected to follow anything that is done and partly because the doing of anything worth while will mean the expenditure of money. If Australia is neglectful of the international needs of practising doctors as things are today, she will have no right to expect other nations near at hand to take notice of her when medical practice is in difficulty in any future stage in international evolution. Australia has appealed to the imagination of the World Medical Association because of recent medico-political success in matters affecting the Government and the profession. An Australian doctor has been appointed to the Council of the World Medical Association, in the person of Dr. L. R. Mallen, who by reason of his experience as a member of the Federal Council and of the South Australian Branch Council is well qualified to represent the practising profession of this country. Dr. Mallen attends the meetings of the Council of the World Medical Association as they are held from time to time in different parts of the world. The Federal Council has made an error in judgement in thinking that he should also act as delegate from the Federal Council at the next meeting of the World Medical Association, to be held at Athens in October, 1952. This decision, if it is allowed to stand, is, to say the least of it, penny wise and pound foolish and will not be looked on with favour by other nations represented at the meeting. The prestige of the Australian medical profession is at stake, apart from any consideration of the need to adopt the long-range statesmanlike view.

Current Comment.

"MYSOLINE": A NEW ANTICONVULSANT.

A DRUG not yet freely available, "Mysoline", produced by Imperial Chemical (Pharmaceuticals), Limited, is a new anticonvulsant for use in the treatment of epilepsy. Although closely related to phenobarbitone, it is of a chemical type not hitherto used in man, its chemical name being 5-phenyl-5-ethyl-hexahydropyrimidine-4:6-dione. It is a white crystalline substance, practically tasteless, chemically stable, and sparingly soluble in water. It was first developed and synthesized in 1949 by Bogue and Carrington. A full clinical trial on 40 epileptic patients at the David Lewis Epileptic Colony was carried out during 1951 by R. Handley and A. S. R. Stewart.[1] Their results confirm the earlier animal experimental conclusion of the drug's particular efficacy against *grand mal* attacks. Its toxicity is extremely low and it has almost no hypnotic action. The 40 patients in this trial had been in the colony for many years, the incidence of fits during the previous few years had been carefully recorded in each case, and the condition of the patients at the start of the trial was the best that could be achieved with existing anticonvulsant drugs, either alone or in combination. At first half this group received inert tablets indistinguishable from those containing the active drug; however, this control was soon suspended because the improvement of those treated was so great as to make it virtually certain that the drug was responsible, and the control group realized that the other half were getting better while they were not. Thereafter "Mysoline" was given to all 40 patients In changing to the new treatment, a dose of 0·2 gramme of "Mysoline" twice daily was first added to whatever was being given at the time. It is recommended that the previous drug should be withdrawn gradually over a period of two weeks, by which time the daily "Mysoline" dose should have been increased to 1·0 gramme. This can then be further increased. The optimum daily dosage of "Mysoline" rarely exceeded 1·6 grammes, increased control by larger doses being sometimes offset by undesirable symptoms. At the commencement of treatment several patients complained of dizziness, accommodation disturbances, listlessness, and difficulty in rousing from sleep; but all these symptoms passed off in a few days and treatment was not interrupted. Regular urine examinations and full blood counts in all cases did not reveal any abnormality. Of the 40 patients, 32 were improved and 12 were completely free from attacks of all kinds. Results were assessed over a period of six months, and by doubling the number of fits during this period, comparisons were made with the previous year as to the

[1] *The Lancet*, April 12, 1952.

incidence of fits. Only 20% of patients were not improved. Generally speaking those with severe mental deterioration did not respond so well. Some additional benefits were noted: a feeling of fitness, an improved ability to perform small tasks, mental alertness instead of the former dulness, and a new interest in pastimes, such as dancing.

If Handley and Stewart's encouraging results in this small series of cases are confirmed by more extensive trials, and if prolonged use of "Mysoline" does not result in a tapering-off of early effects and late toxic side-effects, a notable improvement in the control of major epilepsy will have been achieved. The action of "Mysoline" in other types of epilepsy may also be worthy of study.

MENINGITIS DUE TO HÆMOPHILUS INFLUENZÆ.

IT is only a few years since review of the local literature showed how seldom recovery took place from meningitis due to *Hæmophilus influenzæ*. Though this organism now parades under an inappropriate name, it is none the less serious in the damage it can inflict upon the nervous system, particularly of young children. Now the antibiotics have changed the outlook from that of an almost uniformly lethal disease to one from which the patients recover more often than not, though intracranial complications may occur. E. B. Schoenbach, H. C. Spencer and Jacques Monnier have published a series of thirty consecutive cases of this disease.[1] They point out that it is the commonest of the bacterial forms of meningitis except the epidemic meningococcal variety, and that it may occur as a sequel to local cranial disease or trauma or, more frequently, may arise apparently from some blood infection associated with respiratory disease. Experimental work has shown that aureomycin and chloramphenicol can protect mice from *H. influenzæ* infection, and clinical trial in the human subject more than bears out the promise in animals.

The present study was carried out at the Johns Hopkins Hospital. Eighteen patients were treated with aureomycin and sulphadiazine, and twelve others with chloramphenicol alone. The diagnosis was established by examination and culture of the spinal fluid obtained by lumbar puncture, and Gram-negative pleomorphic bacteria when found were tested against type B specific rabbit antiserum. The sensitivity of the organisms was then ascertained to all the antibiotics. The dosage of aureomycin and chloramphenicol, as also that of sulphadiazine, was calculated according to the body weight; it will be noted that the patients were all very small children, usually infants. The initial dose of aureomycin was usually 40 to 100 milligrammes per kilogram, given intravenously; later doses were given subcutaneously. Sulphadiazine was given by mouth as soon as practicable in doses of 150 to 300 milligrammes per kilogram of body weight. Chloramphenicol, used in the later series, was given by parenteral as well as oral routes; half the patients were treated solely by the oral method. Successful treatment soon produced sterilization of the cerebro-spinal fluid, but there was some variation in the results of culture in different patients. The authors describe in detail illustrative cases which emphasize the need for careful and regular observations of the spinal fluid, and of the clinical state of the patient. In some of those treated with aureomycin and sulphadiazine prompt response and satisfactory recovery took place. Relapse was seen in one patient, but assiduous treatment produced recovery without sequelæ. The children treated with chloramphenicol usually showed prompt response also, but both groups contained instances of a serious complication, subdural effusions. Of course, the history of antibiotic treatment of meningitis has already warned us of this possibility. In the early days of penicillin the association of Cairns with the team showed how important and serious localized intracranial effusions could be, and how essential it was that antibiotic and surgical treatments should be used in combination when necessary. Schoenbach and his colleagues in their series found subdural effusions in some children which sometimes needed repeated tapping by various routes. The fontanelles could sometimes be used, or burr holes in the skull. The overall results showed recovery of fifteen of the first eighteen, only two deaths being attributable to the infection, and all twelve patients in the second subseries recovered. Five patients of the first eighteen showed residual damage to the nervous system, and two of the last twelve. The numbers are probably not large enough to be statistically significant as to the superiority of chloramphenicol. Since the natural complications may include hemiplegia or cranial nerve damage, they are of great importance, and point to the need for early and efficient treatment. The last warning of the authors reemphasizes the necessity for looking for subdural effusions, remembering the pyogenic capacity of the infecting organism.

[1] *The American Journal of Medicine*, March, 1952.

IMMUNIZATION AGAINST INFLUENZA.

THE problems of epidemiology and the public health have been studied more intensively since military applications of their solution have become of special importance. The offices of the Surgeon-General, United States Army, lend assistance to workers in projects of such nature, and their Commission on Influenza has produced several major contributions. The May, 1952, number of *The Journal of Experimental Medicine* has an important paper on the use of adjuvants in studies on influenza immunization by Jonas E. Salk and Angela M. Laurent, which marks a considerable advance. Hitherto attempts to induce artificial immunity to the influenza virus have been limited by two factors, its short duration when produced by simple saline suspensions of virus particles, and the undesirable local reactions at the site of inoculation when other substances were incorporated in the injected fluid. The most recent studies have added killed acid-fast bacilli as adjuvants, and although this improved the duration of the immune response, it also provoked local reactions of some severity in the experimental animal.

Salk has substituted as adjuvant a mineral oil and an emulsifying agent which produced no local irritant effect, and at the same time maintained an antigenic response of high order for so long a period as fifty-two weeks. He worked with rhesus monkeys, and controlled the effects of his immunizing injections given intramuscularly, by observing the serum activity in virus neutralizing power in the fertile egg, hæmagglutination of chicken cells, and complement fixation in the presence of a virus antigen. Several interesting observations were made on the tissues after some months. Histological examination showed that a wide area exhibited the finely divided oil surrounded by large collections of lymphocytes and monocytes, constituting what the author styles an "antibody producing organ"—in contrast to the cystic structure localized in a small area after subcutaneous inoculation. The estimation of antibody levels revealed that the rises demonstrated by the three techniques took place at somewhat different rates—hæmagglutination first, neutralizing power a little slower but to a higher level, and complement-fixing activity more slowly, and tending to fall over the period of observation. The actual levels obtained were many times higher than in animals immunized with the same amount of antigen in an aqueous solution and the dose of virus could be suspended in one-tenth the volume of adjuvant and still produce an equally high response.

There is considerable interest in the suggestion that the antibodies are independent of one another or at least develop at different rates, and this aspect of the work is being pursued further. Of considerable practical importance is the observation of the height and persistence of antibody produced in this manner, because a year's protection is a worthwhile object to attain in contrast to previous methods which at most could be shown to last three months. Finally the absence of untoward reactions at the site of inoculation justifies a trial of the method in human volunteers, particularly since there is evidence that an inoculum so small as 0·1 millilitre will produce high levels of antibody, and facilitate study of the relationship of these antibodies to infection.

Abstracts from Medical Literature.

PHYSIOLOGY.

In-Vivo Uptake of Cations by Two Types of Exchange Resins.

E. W. McCHESNEY (*The American Journal of Physiology*, January, 1952) reports a study of the uptake of cations by sulphonic and carboxylic types of ion exchange resins in rats. He states that the evidence indicates that both resins remove from the food sodium, potassium, calcium and magnesium, but no amino acids, thiamine or riboflavin. The fæcal iron output of the resin-treated animals is slightly greater than that of the controls, but is insignificant in terms of milliequivalents per gramme of resin. Total extrafæcal cations (exclusive of ammonia) average 1·8 milliequivalents per gramme for the sulphonic resin. Evidence based on the effect on acid-base balance of feeding various proportions of the sulphonic resin in the sodium or potassium cycle also indicates that its total uptake of fixed base is 2·4 milliequivalents per gramme. It is suggested that for both resins the total uptake is a resultant of an equilibrium established by the competition of all ions, including those released from the resin in the exchange. The ratio of sodium to potassium uptake of the resins always exceeds the dietary ratio of these elements. This does not support the idea that the exchange reaction is limited to the upper portion of the small intestine.

Intestinal Absorption of Sodium Chloride Solutions.

D. D. BLICKENSTAFF, D. M. BACHMAN, M. E. STEINBERG AND W. B. YOUMANS (*The American Journal of Physiology*, February, 1952) report a study of the absorption of sodium chloride solutions in three dogs with upper jejunal fistulæ. A description of the Omi-type of fistula is given. The absorption periods lasted thirty minutes, and measurements were made of net water and chloride absorption. During the experiments the intraluminal hydrostatic pressure of the test solutions was maintained at a given level by the use of a burette-catheter system. Two main variables were studied: intraluminal pressure and concentration of sodium chloride solution. The findings were as follows: (i) There were statistically significant differences in the mean rates of absorption of chloride and water at different levels of hydrostatic pressure; between the extremes tested there was an optimal pressure at which absorption was most rapid. (ii) Water was absorbed more rapidly from dilute solutions than from concentrated solutions. (iii) There were no statistically significant differences in the rate of chloride absorption from the five solutions of different concentration.

Absorption of Water and Chloride.

E. F. ADOLPH AND J. P. NORTHROP (*The American Journal of Physiology*, February, 1952) report that the walls of the alimentary tract of rats showed appreciable swelling when fluids were placed in the tract. The passage of fluids along the tract depended on their concentrations of salt. For equal excesses of water to gain access to the body from alimentary tract and from peritoneal cavity, more water had to be administered by the latter route. By it more chloride was withdrawn from the body. Hypertonic salt solution when placed in either alimentary tract or peritoneal cavity drew large volumes of water into it before absorption of salt became appreciable. Adaptation was not found in absorption of the doses of water that were tested when rats were previously subjected to excesses of water at either site of administration.

High Altitude and Longevity.

P. D. ALTLAND AND B. HIGHMAN (*The American Journal of Physiology*, February, 1952) report the effects of exposure to a simulated altitude of 1800 feet upon the life history of 53 male and female rats. Exposures were continued for four hours daily from the age of fourteen to five hundred and forty days, and the observations were continued until death. The exposed rats lived as long as their unexposed controls. There was a proportionate increase in the hæmatocrit values and in the hæmoglobin content of the blood of exposed rats, with males reaching higher levels (hæmatocrit value, 78; hæmoglobin value, 23 grammes per 100 millilitres) than females (hæmatocrit value, 70; hæmoglobin value, 20 grammes per 100 millilitres). These blood values were generally maintained at relatively constant high levels during the first year, after which a pronounced decline was observed. Eighty-two additional exposed rats and 61 unexposed rats were killed for histopathological study. Pathological changes were generally much less severe than those reported at 2500 feet. The rats exposed to 1800 feet showed no significant increase in the weight of the heart and adrenal glands and no thymus atrophy. However, some showed fatty degeneration and hæmosiderosis of the liver and kidney, and some had significant fatty changes in renal vessels. There was general congestion with an increase in the size of the renal glomeruli, apparently due chiefly to capillary engorgement. Because of the increase in hæmatocrit values, there was an increase in the capillary and erythrocyte surface areas per unit of plasma. The importance of these changes in the diffusion of gases and other substances to and from the bloodstream during exposure to high altitude is discussed.

Mechanisms of Production of the First Heart Sound.

A. A. LUISADA, M. M. ALIMURUNGA AND L. LEWIS (*The American Journal of Physiology*, January, 1952) report an investigation of the first heart sound with the technique of stethoscopic and logarithmic phonocardiography. A series of open chest experiments was made in order to study the mechanism of production of the first heart sound, under the following conditions: (*a*) in the empty heart, (*b*) after ligation of the atrio-ventricular groove, (*c*) after extensive damage of the atrio-ventricular valves, (*d*) after the ligation of the large arteries, and (*e*) after necrosis of the ventricular walls. Phonocardiograms were recorded together with either the cardiac volume or the left ventricular pressure. The experiments did not allow the separation of the vibrations arising in the valves from those arising in the cardiac muscle, as it was impossible to alter ventricular pressure without changing the force of closure of the atrio-ventricular valves, nor to damage the atrio-ventricular valves without altering the ventricular pressure. Studies were performed on normal human subjects by recording the low frequency (apical cardiograms) and the high frequency vibrations (phonocardiograms) of the chest wall; and on normal dogs and rabbits by recording left ventricular pressure and phonocardiograms. The studies confirm the existence of two groups of vibrations within the first sound. These two groups of vibrations coincide with the two main valvular events of early systole (closing of the atrio-ventricular valves and opening of the semilunar valves) and with two distinct waves in the low frequency tracing of the chest (apex cardiogram). It is suggested that the first sound is the result of a combination of muscular and valvular factors. Sudden changes in muscular tension activate first the atrio-ventricular valves and then the semilunar valves. This rapid succession causes a double vibration of the cardiac wall and is further transmitted to the chest wall including high-pitched (sound tracing) and low-pitched (cardiogram) components. Although simultaneous with the action of the valves, these vibrations are likely to arise in both the valvular and the muscular structures as a response to rapid changes in tension and pressure. Smaller vibrations, possibly of muscular origin, may be seen at times between the two main groups of vibrations of the first sound. Vascular vibrations occur only later, after the beginning of ejection, and have a lower pitch and lesser amplitude.

BIOCHEMISTRY.

Testosterone.

C. D. WEST AND L. T. SAMUELS (*The Journal of Biological Chemistry*, June, 1951) have demonstrated enzyme systems involved in the catabolism of testosterone in the kidney tissue from dog, rabbit and guinea-pig. They state that the principal action of the kidney enzyme systems in all three species was to oxidize the hydroxyl group on C-17 to a ketone. DPN was a cofactor in the dog and guinea-pig kidney system, but not in that of the rabbit. Steroid substrate specificity was studied. The same oxidative system appeared to act on any 17-hydroxy-C19 steroid which had an alcohol or ketone group on C-3. The reaction could be reversed in the presence of acids of the citric acid cycle. Dog kidney tissue also destroyed the $\alpha\beta$-unsaturated ketone structure in testosterone. Citrate had no effect on this reaction. This activity was absent in rabbit and guinea-pig kidney.

Corticoids.

C. D. KOCHAKIAN AND E. ROBERTSON (*The Journal of Biological Chemistry*, June, 1951) have reported that the stimulation of rapid glyconeogenesis in mice by corticoids did not alter the arginase activities of the liver or kidneys. On the other hand, a subcutaneously implanted pellet of 11 - dehydro - 17 - hydroxycorticosterone acetate produced significant increases in both tissues after two days. The same increases were obtained when the determinations were made with either cobalt chloride or manganese chloride

as the enzyme activator. The alkaline phosphatase of the liver was not increased until after seven days. The body weight of the treated mice decreased very sharply, accompanied by an increased nitrogen excretion, a complete disappearance of the thymus and a maximum decrease in the size of the spleen, but the food intake was increased about 20%, and after seven days the extra protein catabolism was no longer evident and the loss in body weight abruptly ceased. The implantation of 11-dehydro-corticosterone as a pellet produced effects qualitatively similar but quantitatively much less than those of 11-dehydro-17-hydroxy-corticosterone acetate. A pellet of 11-desoxycorticosterone acetate produced a small increase in kidney weight and a small decrease in liver arginase, but 11-desoxy-17-hydroxycorticosterone was ineffective.

Linoleic Acid.

G. MEDES *et alii* (*Archives of Biochemistry*, June, 1951) have produced low dienoic acid content of animal tissues (rats) in two ways: first, by withdrawal of essential fatty acid from the diet, and second, by exclusion of pyridoxine or thiamine from the diet or by severe restriction of food (caloric deficiency). With the first method the dienoic acid content of the tissues fell to lower levels, and typical symptoms of the deficiency were produced. With the second procedure, the fall was more rapid in relation to the acute vitamin deficiencies, but no symptoms characteristic of linoleic acid deficiency occurred. A similar but less rapid course was followed in caloric restriction. Since no essential difference in dienoic acid content of the tissues of rats was found under these several dietary conditions, it was concluded that pyridoxine under the conditions of these experiments does not exert a special supplementary action in the production or conservation of polyenoic fatty acids.

DDT.

C. D. JOHNSTON (*Archives of Biochemistry*, May, 1951) has reported that DDT and several of its related compounds were inhibitory to rat heart succinic oxidase at concentrations of from 10^{-4} to 10^{-5} M, the degree of inhibition being about 70% to 90% at the higher concentration. The inhibition could also be shown for cytochrome oxidase, but not for succinic dehydrogenase. The inhibition was demonstrable when the insecticide or its derivatives were added to the enzyme system as alcoholic solutions. Cholesterol at the same concentrations did not inhibit succinic oxidase. When DDT was present as an oil emulsion, only a slight inhibition could be shown towards the succinic oxidase system, even though the concentration in the emulsion was ten times that of the highest level in alcohol. DDA, the acetic acid derivative of DDT, and a known metabolite thereof, was much less inhibitory towards the succinic oxidase and cytochrome oxidase systems, even at a concentration of 5×10^{-4} M.

Pantothenic Acid.

R. E. OLSON AND F. J. STARE (*The Journal of Biological Chemistry*, May, 1951) have demonstrated that the coenzyme *A* content of cardiac auricle and ventricle is reduced 40% to 80% by pantothenic acid deficiency in ducklings. Both in normal and in deficient animals, ventricle contained twice as much coenzyme *A* as auricle. With pyruvate as substrate, the oxygen consumption and net pyruvate utilization of slices of ventricle and auricle were significantly reduced in pantothenic acid deficiency, but not in proportion to the decrease in coenzyme *A* content. The data support the view that the function of coenzyme *A* in the pyruvate metabolism of cardiac muscle is to catalyse the condensation of the C_2 fragment derived from pyruvate with oxaloacetate to yield citrate.

Ascorbic Acid.

J. J. BURNS *et alii* (*The Journal of Biological Chemistry*, August, 1951) have carried out metabolic studies by administering radioactive ascorbic acid to guinea-pigs which had received various daily supplements of ascorbic acid. The C^{14} in respiratory carbon dioxide and urine was determined over periods of twenty-four hours and ten days. The authors state that the conversion of ascorbic acid to carbon dioxide is a main pathway of its metabolism in guinea-pigs. The large amount of C^{14} found in calcium oxalate isolated from guinea-pig urine indicates that oxalic acid is an end product of ascorbic acid metabolism. The direct or indirect synthesis of oxalate from glucose by guinea-pigs was also confirmed. The overall distribution of C^{14} in the tissues of the guinea-pig was approximately the same as that found by the chemical analysis for ascorbic acid. No great differences were found in the distribution of C^{14} in organs and tissues of normal and scorbutic guinea-pigs. There was no detectable incorporation of C^{14} into liver glycogen. The teeth were found to have a higher specific activity than such organs as liver, adrenals and spleen. The nature of C^{14} incorporation into cartilage and skin was studied. No measurable radioactivity was found in chondroitin sulphate or collagen fractions isolated from those tissues. Essentially, all of the C^{14} found in nasal septum and skin was readily extractable with water or 8% acetic acid solution. Evidence from carrier-dilution experiments shows that essentially all the C^{14} measured in the nasal septum is present as ascorbic acid.

Adrenaline.

R. W. SCHAYER (*The Journal of Biological Chemistry*, October, 1951) has synthesized *dl*-adrenaline labelled in the methyl group with C^{14}. A significant percentage of the methyl carbon of adrenaline administered to rats is oxidized to carbon dioxide. After intravenous injection of small quantities of B-C^{14} adrenaline, no conjugates could be detected in the urine of rats and only traces in the urine of rabbits; this indicated that conjugation is not a route of adrenaline inactivation under physiological conditions. After the feeding of large quantities of B-C^{14} adrenaline to a rat, a considerable amount of conjugated adrenaline was found in the urine, the conjugation occurring presumably in the intestine or liver. Although all the C^{14} of small quantities of B-labelled adrenaline is excreted in the urine by rats and rabbits in as little as four hours, the C^{14} of methyl-labelled adrenaline is only slightly more than one-half excreted under similar conditions. It is concluded that a reaction or reactions involving cleavage of the molecule at some point between the B-carbon and the methyl carbon constitutes a major pathway of adrenaline metabolism. Urine from rats and rabbits receiving B-C^{14} adrenaline has significant amounts of radioactivity in the ether-soluble fractions; ether extracts of urine of animals given methyl C^{14} adrenaline are completely free of radioactivity. At least two ether-soluble adrenaline metabolites are formed. It is concluded that these substances are formed from adrenaline by loss of methylamine.

Cortisone.

W. UMBREIT AND N. TONHAZY (*Archives of Biochemistry*, June, 1951) have presented data demonstrating that the D-amino acid oxidase of rat liver is lowered as a result of adrenalectomy and restored to normal by treatment with cortisone. They state that this reaction is responsible for data obtained which indicated that creatine and creatinine formation were under the control of cortisone. The α-keto-γ-methiolbutyric acid formed from the oxidation of methionine reacts in the Jaffe reaction as "creatinine". During the course of the liver enzyme system a portion of the α-keto-γ-methiolbutyric acid appears in a bound form and is measured by way of the Jaffe reaction as "creatine". Measurements of creatine formation by a method not subject to these errors show that creatine formation in the rat liver enzyme is very small, although creatine formation in guinea-pig liver can readily be demonstrated.

Pituitary.

E. ADAMS AND E. L. SMITH (*The Journal of Biological Chemistry*, August, 1951) have shown that aqueous extracts of several pituitary preparations contain a variety of exopeptidases. Similar extracts of lyophilized anterior pig pituitary contain at least two proteinases. Synthetic substrates known to be hydrolysed by cathepsins and proteinases of the gastro-intestinal tract are not attacked by either pituitary proteinase. Purified hog ACTH, which yields negative findings in tests for peptidase activity with several substrates, contains contaminating quantities of pituitary proteinase, which may explain certain features of ACTH instability as measured by bioassay.

Proteolipides.

J. FOLCH AND M. LEES (*The Journal of Biological Chemistry*, August, 1951) have demonstrated that tissues contain substances to which the name of proteolipides has been given. These are lipoproteins which exhibit solubilities quite different from the solubilities of other known lipoproteins. Thus while the latter are usually soluble in water or dilute salt solutions, proteolipides are insoluble in water and freely soluble in chloroform-methanol-water mixtures. Proteolipides are present in the following tissues that have been studied and are listed in order of decreasing content of proteolipides: brain white matter, brain tumours, brain grey matter, heart, kidney, liver, lung, smooth muscle, skeletal muscle. They are absent from blood plasma. From white matter three different proteolipide fractions have been isolated.

Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

XXIX.

THE BILIOUS ATTACK.

ALL medical practitioners are familiar with the phrase "a bilious attack". Patients often say that they have suffered from bilious attacks since childhood. These bilious attacks are almost invariably migraine. A careful history usually reveals an hereditary taint, and a story of visual disturbance and headache associated with the biliousness or vomiting.

Migraine headache usually begins on waking in the morning. It may, however, commence during the day. It is a dull pain referred to the forehead or occipital region on one side, occasionally on both sides. Sometimes the pain is all over the head. The headache may last two or three hours up to several days, though rarely more than three days. The headache may be slight, or very severe and incapacitating. It is usually associated with pallor, and the patient may feel completely drained of strength. The frequency of the headaches varies greatly—at first every few months and later every week, or even two or three times a week. After middle age they often cease. Various sensory auræ occur as a rule associated with the headaches. Frequently a visual disturbance occurs—indistinctness of vision, hemianopia, a sensation of something streaming down before the eyes, a narrowing of the visual fields, and rarely, fortification spectra. In so-called ophthalmoplegic migraine visual defects may occur without headache; other sensory auræ such as numbness and tingling in the hand, spreading to the lips and tongue, may occur. These sensory phenomena may continue for several minutes up to an hour.

Motor phenomena are exceedingly rare, but aphasia, especially difficulty in recalling names of objects or people, may occur. The headache may be preceded by lassitude, lack of concentration or emotional upset. After the visual aura comes nausea, often followed by vomiting for some hours. There may be no vomiting, but nausea is almost invariable; salivation, sweating, coldness and pallor usually occur.

Ophthalmoplegic migraine is said to be associated with lesions of the oculomotor nerve or aneurysms of the cerebral vessels at the base of the brain.

Abdominal migraine and psychic migraine are doubtful entities. Migraine is a French word, but the complaint also bears the Latin name hemicrania, signifying one side of the head. The popular names bilious headache, bilious attack, blind headache and sick headache are all based on the symptoms which occur in the majority of patients. The term bilious was derived partly from the fact that bile was often vomited, and partly from the humoral pathology, in which bile was regarded as one of the chief morbific fluids of the body.

The disorder is often associated with high intellectual ability, and many distinguished scientific men have suffered from it, and have supplied more careful observations of the subjective symptoms than we possess of any other malady.

There are no other conditions referred to as bilious attacks. Patients may speak of their liver being out of order, or may describe attacks of cholecystitis or biliary colic, but the term bilious attack is not applied to these.

Diagnosis of migraine is usually not difficult if a careful history is taken, and physical examination reveals no evidence of organic disease. In childhood, however, great care must be taken in excluding organic diseases. Many childish disorders are associated with vomiting, and the visual disturbances and headaches of migraine are less apparent in childhood. This may be because children are not good at describing their symptoms.

Neuralgia of the fifth nerve and of the second occipital nerve, the latter often associated with fibrositis of the trapezius, may cause difficulty in diagnosis. However, in neuralgia the pain is often shooting or stabbing, and is not associated with visual disturbances or vomiting. Conditions such as sinusitis are preceded by an infection of the nose or throat. Cerebral tumour is seldom accompanied by symptoms of migraine, but must, of course, be borne in mind. Headache in hypertension and renal disease should be excluded by the accompanying signs. Eye strain by itself usually causes headaches in the afternoon, or after much use of the eyes for close work, or in a poor light.

A diagnosis of epilepsy or *petit mal* has been made in cases of migraine, though a knowledge of the two should prevent such a mistake. The course and prognosis of migraine vary greatly. The condition may die out in later childhood, and recur in middle life. Women at the menopause often suffer severely. Anxiety and overwork aggravate the condition.

There has been a great deal of work done to try to ascertain the cause of migraine. Apart from the fact that women are said to be affected more often than men, in the proportion of five to four, more or less, and that the condition is frequently inherited, little has been discovered. Investigations have not proved that dietary factors play much part. Duodenal stasis has been demonstrated by X rays, often with regurgitation of the duodenal contents into the stomach. These observations made during an attack suggest that the stasis was more likely to be the result than the cause of the migraine.

Swelling of the *hypophysis cerebri* has been advanced as a cause, and radiographs showing a small pituitary fossa or overlapping clinoid processes have been demonstrated, but these changes often appear normally.

Eye strain is not the cause of migraine, but astigmatism, defective muscle balance, close work or bad light may be aggravating factors. At present vasomotor influences associated with contraction, followed by dilatation, of the cerebral blood vessels, mainly at the surface or at the base of the brain, are thought to be the cause of the symptoms.

The diagnosis of migraine having been made, evidence should be sought of eye strain, or of possible relationship to certain foods. Patients often suspect fatty foods, and they may be a cause. Others say that eggs, apples, oranges and other foods bring on the attacks. It is best not to argue with the patients; they may be right. Skin tests for allergic response have been of little value up to the present time. Some patients wish to have an X-ray examination of the head, and there is no harm in this.

Treatment has varied with the times. In a recent review of 600 patients A. P. Friedman and T. von Storch stated that placebos relieved 20% of their patients. They considered that ergotamine derivatives were best for symptomatic relief, and that ergotamine and caffeine combined ("Cafergot") gave the best results of all. The authors mentioned nicotinic acid, thiamine chloride, testosterone and antihistaminics as being of little value. Intravenous and subcutaneous injections of histamine were said to prevent the headaches in 36% of their patients. Psychotherapy was the most effective preventive, in the opinion of these authors. They did not state the type of psychotherapy, nor the duration of such treatment. Physical therapy was unsatisfactory in those cases in which it was tried. The views expressed as to the value of histamine injections and psychotherapy are not supported by the experience of others. However, the usual psychotherapeutic approach is necessary in migraine, as in all other maladies.

Usually, when the patient is examined, many treatments have been tried. Phenobarbital in doses of half a grain or less thrice daily may be of use at times. Soluble phenobarbital (three grains) given intramuscularly may relieve severe and prolonged vomiting. Aspirin, phenacetin, and combinations of these drugs relieve some patients. Ergotamine tartrate in doses of 0·5 milligramme often affords relief when given hypodermically, and sometimes when given by mouth. The most effective preventive treatment, even to this day, is probably the mixture prescribed by Sir William Gowers, containing *Liquori Trinitrini* one to two minims, *Tincturæ Gelsemii* 10 minims, *Tincturæ Nucis Vomicæ* 10 minims, *Syrupi Limonis* 15 minims, *Sodii Bromidi* 10 grains and *Aquam Chloroformi* to two drachms. Two fluid drachms to be taken three times a day in water for six weeks.

Trinitrin should be given in doses of one minim at first. The patient should be warned that it may cause a thumping in the head, and advised to sit down quietly for some minutes after taking the mixture. The mixture is not helpful during an attack. Increase of the dose of trinitrin to one and a half or two minims may be tried, if relief is not obtained with the smaller dose. No attempt is made to defend this prescription on pharmacological grounds. In the hands of the author it has appeared to work.

G. C. WILLCOCKS,
Sydney.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held at the Medical Society Hall, Albert Street, East Melbourne, on March 5, 1952, DR. CHARLES BYRNE, the President, in the chair.

Radioactive Iodine and Thyroid Disease.

A symposium was presented on "The Use of Radioactive Iodine in the Treatment of Thyroid Disease".

DR. R. KAYE SCOTT spoke on the scope and uses of radioactive iodine and described the work which had been carried out at the Royal Melbourne Hospital. A report of this work was recently made to the Anti-Cancer Council of Victoria and was published in THE MEDICAL JOURNAL OF AUSTRALIA on December 29, 1951, at page 887.

MRS. D. WINIKOFF, of the Department of Biochemistry, University of Melbourne, who presented the biochemical aspect of the subject, opened her contribution with a brief summary of iodine metabolism in the body. She drew attention to the three independent mechanisms in the thyroid gland—(*a*) iodine accumulation, (*b*) hormone synthesis, (*c*) hormone secretion—and said that during those processes inorganic iodide was trapped by the thyroid cell and converted into the organically bound form. The iodinated protein, thyroglobulin, was then stored in the colloid. According to physiological requirements it was subsequently broken down into smaller units and the resulting thyroid hormone entered the blood-stream. Thus, in the blood at any stage, two iodine fractions were coexistent: inorganic iodide, which was incidental, and the more stable organically bound fractions, which could be precipitated with the plasma proteins—protein-bound iodine or serum-precipitable iodine. Protein-bound iodine alone constituted the actual hormonal iodine and was clinically significant as an index of thyroid activity.

In conditions associated with hyperfunction or hypofunction of the gland, values for protein-bound iodine were outside the limits which were generally accepted as normal, namely, from three to eight microgrammes per 100 millilitres of blood. There was, however, a certain degree of overlap between normal and pathological values.

In cases of hypermetabolism or hypometabolism not associated with thyroid diseases, protein-bound iodine remained within normal limits (except during pregnancy). That made it a very useful tool for segregation of non-thyroid diseases with confusing clinical symptoms.

Mrs. Winikoff went on to say that many methods for estimating protein-bound iodine were in existence. Most of them were complicated and required staff trained in microchemical techniques and special laboratory facilities. The method in use at the University of Melbourne was a modification of the method of Barker (United States of America). It required 10 millilitres of blood for one estimation in duplicate.

A serious limitation to the diagnostic value of protein-bound iodine estimation was the effect of various medications. A significant artefactual elevation could be caused by the administration of Lugol solution, thyroid preparations, opaque dyes used in the X-ray examination of the kidney, bronchi and gall-bladder, sea foods, iodized salt, and even cough mixtures and throat tablets. A considerable lowering of the values obtained could be the result of antithyroid drugs, thiocyanate, mercurial diuretics, cortisone and ACTH, and excess of certain vegetables. In most cases the false results could be avoided by allowing a suitable time-interval free from medication. It was advisable to give the patient a standardized diet for a fortnight preceding the test or at least to instruct him to avoid sea foods and excess of fat.

Mrs. Winikoff said that diagnosis based on protein-bound iodine determinations on a group of 44 patients had given approximately 90% agreement with clinical assessment. The group had included many borderline cases. Those results compared favourably with overseas results. Moreover, the clinical assessment could not always be carried out simultaneously with protein-bound iodine estimations, and, since the latter changed more rapidly than the clinical symptoms, some of the failures in agreement could be attributed to that factor.

Mrs. Winikoff concluded by saying that, providing all necessary precautions were observed, protein-bound iodine could be regarded as a reliable aid in assessing the function of the thyroid gland. It was valuable in following the effect of therapy or appraising the success of surgery. It had also the added advantages of causing the minimum of discomfort to the patient and of placing no extra burden on the physician.

MR. K. H. CLARKE, of the Commonwealth X-Ray and Radium Laboratory, in his paper, which was read in his absence by Mr. R. L. Aujard, outlined the physical aspects of the project. He said that radioiodine (I^{131}) was chemically identical with ordinary iodine (I^{127}), and that, as far as was known, biological systems had no means of distinguishing between the two. The fact that iodine was so selectively taken up by the thyroid gland or thyroid functioning tissue enabled some aspects of thyroid function to be studied by determining the uptake of I^{131} by the thyroid, its excretion by the kidneys and the concentration of I^{131} in the blood at various times after administration. By use of the radiation emitted from I^{131}, such determinations could be made with Geiger counters and their associated equipment.

The hyperthyroid gland, whose function had not been influenced by medication, displayed a very rapid initial uptake of I^{131} from the blood, a high maximum and generally a fairly rapid fall. The normal gland displayed a slower initial uptake, rising to a lower maximum and then falling less rapidly; whereas the hypothyroid gland displayed a very slow initial uptake, rising to a low maximum, followed by a steady fall.

Thus, broadly speaking, the characteristics of the thyroid uptake curves could be related to the various functioning states of the gland. In practice, however, there was a certain spreading of the curves within each group with consequent overlapping, and that introduced difficulty in the interpretation of results in borderline cases.

Since the thyroid and kidneys were the main competitors for iodine in the blood, it followed that most of the iodine which was not taken up by the thyroid must be excreted by the kidneys; so it was not unreasonable to expect that the urinary excretion of I^{131} might reflect the functional state of the thyroid, subject to there being no renal disorder. The excretion curves also showed spreading within each group and some overlapping. However, in spite of the spreading there were a number of factors that could be determined from the data mentioned, and some of those, it was believed, might be of value to the physician in diagnosing the functional state of the thyroid. The factors fell into four groups: (i) rate of accumulation of I^{131} by the thyroid for the synthesis of thyroid hormone; (ii) rate of removal of I^{131} from the blood by the thyroid; (iii) rate of output of organically bound I^{131} from the thyroid; (iv) rate of excretion of I^{131} by the kidneys.

Mr. Clarke said that in the present stage of the work they were trying to establish the ranges of values of the factors which corresponded to the various functional states of the thyroid, as assessed by clinical observation, so that the accuracy of the limiting values of each range was dependent, to some extent, on the degree to which borderline cases could be accurately assessed clinically. There was, as was expected, some overlap of values, but the physical measurements had given a correct classification in 80% to 85% of cases. Many of the patients had been treated previously with thiouracil or iodine or thyroid; so that before a sound appraisal of the value of the physical measurements could be made the influence that such medication could have on the results would have to be investigated. An attempt was also being made to determine whether or not retrosternal or substernal masses and metastases from thyroid carcinomata were thyroid functioning. If those masses were thyroid functioning they would take up I^{131}, the presence of which could be detected by a Geiger counter, in which case treatment with therapeutic quantities of I^{131} might follow.

DR. W. E. KING, discussing the medical aspect of the question, said that the role of the physician in dealing with radioactive iodine as a diagnostic test was much more difficult than that of his colleagues. It had been shown that the physicist, the biochemist and the pathologist all had some set result by which they could estimate the degree of hyperfunction of the thyroid gland. For that reason in dealing with borderline cases there must be some overlap in results. Another reason why there would be some divergence in the opinions obtained was that the thyroid gland varied in its function from day to day. Nonetheless it had been found that, with a large number of measurements of uptake, metabolism and excretion of radioiodine, in 80% of cases agreement had been reached by all methods. It was thus seen that, provided allowance was made for applying mathematical equations to the human body, con-

siderable help could be given to the clinician in the diagnosis of doubtful cases of thyrotoxicosis.

Dr. King went on to say that when the present work was commenced it was decided that only patients that were doubtfully "toxic" would be investigated and it was realized that the accuracy of the tests would suffer in comparison with overseas series which comprised a percentage of obviously "toxic" patients. By the present method the answer was not obtained until two weeks had elapsed, but that was to allow the physicists to compare various measurements worked out in England and America with those developed in Melbourne. It was hoped that in the near future, with sufficient material, it would be possible to shorten the tests, and to obtain an answer within two to three days.

When they were dealing with metabolism of small quantities of injected radioactive iodine, care had to be taken to ensure that the patient had not been taking iodine or thyroid for a period of two to three weeks prior to the tests, otherwise false results would be obtained. Therefore, radioactive iodine could not be used as either a diagnostic or a therapeutic measure in patients who were being treated at the time with iodine or antithyroid drugs.

Another diagnostic use had been to assess the degree of increased function in the thyroid in cases of exophthalmic ophthalmoplegia. Even in the post-operative cases the patients had shown some evidence of thyrotoxicosis, and it had been possible to combine X-ray therapy to the pituitary with graded doses of radiolodine to suppress thyroid function.

In the diagnosis of mediastinal tumours, too few cases had been met with for the results to be definite, but the nearness of a functioning thyroid to the retrosternal goitre made the assessment of the uptake difficult.

In therapy with radioactive iodine the cases included had been limited to those in which recognized methods had failed, or had been unsuitable. The therapy was particularly valuable for recurrent thyrotoxicosis after operation, when there had been damage to one recurrent laryngeal nerve. In all, twelve patients had been treated, though in more than half the cases a second therapy dose had been necessary. The reason for that was that it was difficult to assess the mass of thyroid tissue, and they had been content to use rather smaller doses and so avoid the risk of rendering the patient myxœdematous. In assessment of the results of therapy a period of two to three months must elapse before the full effect was apparent. If a second dose was given too soon, then myxœdema might ensue. During the period of waiting it had in some cases been possible to control the patient's condition by the use of thiouracil.

In cases of malignant exophthalmos the results had been encouraging from the combined use of radioactive iodine in small doses and irradiation of the pituitary.

DR. J. A. FORBES, of the Department of Pathology, University of Melbourne, showed histological radioautographs made from thyroid tissue obtained at biopsy or operation and demonstrated human and rat carcinomata analogous in respect of their morphology and ability to metabolize radioactive iodine. Examples were shown to illustrate radioautography as a useful method of investigating the functional aspects of thyroid disease in relation to morphology, and also its limited application in the diagnosis of human thyroid disease in those cases of recurrent and nodular goitre in which the results obtained by more convenient methods, including Geiger counting, were indefinite.

The radioautographs of human and rat carcinomata demonstrated histological types of carcinoma tissue which took up radioactive iodine. "Uptake" was demonstrable in tissue which had become differentiated to form vesicles, however rudimentary, although removal of the thyroid gland, whose avidity for iodine was usually very much greater than that of the carcinomata, was often necessary for the observation of "uptake".

The cellular tumours which contained no demonstrable areas of differentiated tissue showed more rapid growth than the differentiated tumours, were more easily transplanted in animals, and showed no uptake of radioactive iodine. The differentiated tumours also contained cellular areas in which no uptake of iodine was demonstrable. Dr. Forbes said that that observation conformed with the idea that specialized cells metabolized their specialized metabolites (in the present case, iodine) only during the interphase of cell activity (in other words, between successive mitoses) and indicated that radioactive iodine was unlikely to be concentrated in the tumours at the sites of proliferation where the rate of mitosis was high and the interphases were likely to be short in duration. Thus, radioactive iodine appeared to be of use only as a palliative measure in functioning metastases to reduce their size by destroying the differentiated tissue and also to destroy function in the rare cases of thyrotoxicosis through the overproduction of thyroxin by tumour tissue, and not as a curative form of treatment.

The administration of radioactive iodine thus provided a method of treatment theoretically complementary to radiotherapy, which was thought to destroy cells during mitosis. The use of the two methods simultaneously appeared to be indicated in the treatment of carcinomata which possessed thyroid-like function.

Radioautographs and photomicrographs of thyroid glands and thyroid carcinomata of rats treated with therapeutic doses of radioactive iodine demonstrated stages in the destruction of tissue in which the material was localized. The consequent inflammatory reaction was minimal. Apparently local blood vessels were also involved and absorption was slow, calcification of debris occurring in many cases.

A MEETING of the Victorian Branch of the British Medical Association was held at Warrnambool on Saturday, March 29, 1952, DR. CHARLES BYRNE, the President, in the chair. The meeting took the form of a series of clinical demonstrations at the Warrnambool Base Hospital during the afternoon and a lecture by Professor E. S. J. King during the evening.

Gastric Tumours.

DR. J. K. GARDNER presented a series of three patients with gastric tumours. The first was an unmarried woman, aged sixty-six years, with a history of vomiting copious amounts of blood. There was no previous dyspepsia, and no loss of weight had occurred. She had had previous hæmateses approximately six and fifteen years before, and for the last four years had been undergoing treatment for pernicious anæmia. On admission to hospital she was pale and shocked, and an abdominal tumour was palpable for three to four fingers' breadth below the left costal margin. Her condition was improved by blood transfusion, and the results of subsequent investigations were negative except for the barium meal examination which showed a large filling defect of the stomach apparently due to extrinsic pressure. Laparotomy was decided upon, and a large mass was found deep to the stomach. This was a multilobular vascular tumour attached to the gastric wall by a pedicle in the lesser curve in its middle third. A segmental sleeve resection of the stomach including the tumour was followed by an end-to-end anastomosis. The pathologist reported a leiomyoma with degenerative changes and no evidence of malignant change.

Dr. Gardner's second patient was a man, aged sixty-two years, who had vomited "coffee grounds" four days before admission to hospital. During the last four weeks he had had several giddy turns, but there was no history of previous indigestion, pain or loss of weight. On admission to hospital, he was pale, with a hæmoglobin value of 32%. General examination otherwise revealed no significant lesion. He was given a blood transfusion, and after this a barium meal examination, which showed a possible filling defect in the *pars media* of the stomach. A further examination two weeks later revealed an oval, smooth defect still present, which was reported as a possible extramucosal intramural benign tumour. Laparotomy displayed a mobile rubbery tumour the size of a walnut, and the tumour was visualized through an anterior gastrostomy incision. There was some ulceration of the mucosa but no infiltration, and a segment of the stomach, including the tumour, was removed. Macroscopically the tumour was a leiomyoma, but, for regrettable reasons, the specimen did not reach the pathologist for microscopic confirmation.

Dr. Gardner's last patient was a married woman, aged thirty-one years, who had been admitted to hospital complaining of painless projectile vomiting occurring immediately after food for the past two months; she had also lost weight. A barium meal examination showed persistent narrowing of the *pars media*. She was started on an ulcer regime, and about two weeks after her admission to hospital a vague mass was palpable in the left upper part of the abdomen. Investigations yielded negative results except for the presence of occult blood in the fæces. A further barium meal examination showed a persistent smooth filling defect on the greater curve in the *pars media*, and the presence of a benign gastric neoplasm was suspected. Laparotomy showed a contracted, thickened and leathery stomach with

some hard glands along the lesser and greater curvatures. Total gastrectomy was performed, followed by œsophago-jejunal anastomosis. The pathological report on the specimen showed a diffusive infiltration of all coats of the stomach with clumps of deeply staining cells containing numerous mitotic figures. Signet-ring cells were present, and the condition was reported as an adenocarcinoma of the stomach diffusely infiltrating the wall of the stomach.

PROFESSOR E. S. J. KING congratulated Dr. Gardner on his series of cases. He mentioned the fact that benign gastric tumours made up less than 10% of gastric neoplasms. He agreed that the second case presented all the features of a benign tumour. The group as a whole varied, but Professor King thought that most were innocent. The structure was a varied one, but from his experience most were myomata. With regard to the last case, the question arose as to whether the tumour was a true adenocarcinoma. The answer, after microscopic examination, had to be "yes".

DR. S. C. FITZPATRICK asked where the bleeding point was in the first case. With regard to the origin of such a bleeding point, he remembered a man of seventy-two years who had bled profusely from the stomach on the twentieth post-operative day. He had a leiomyoma one inch to one and a half inches in thickness, which had ulcerated in the centre, and he was bleeding from this.

In reply, Dr. Gardner said that he presumed that the bleeding came from a small sinus in the tumour, which was very vascular.

Hydatid Cysts of the Chest.

DR. S. C. FITZPATRICK showed a boy, aged four years, who had presented with abdominal pain. During routine examination areas of dulness were found in the left side of his chest, and X-ray examination showed three hydatid cysts in the left side of the chest and one in the right. The cysts were of approximately the same diameter (or the same age), and it was necessary to decide (i) the site to be operated upon first, (ii) the number of cysts to be removed at one operation, (iii) the interval necessary before operating on the other side, and (iv) the means necessary for prevention of anaphylactic shock. It was decided to operate on the left side first, and it was found possible, by rotating the lobes of the left lung, to remove all three cysts through one thoracotomy opening. Post-operatively, the child developed measles, and the operation on the right side was therefore postponed. Casoni tests done at intervals of two days showed an increase of sensitivity. An attempt was then made to estimate the degree of protection given to the patient by the use of antihistamines.

Dr. Fitzpatrick demonstrated by strip film the various procedures of the two operations.

DR. C. B. BERRYMAN congratulated Dr. Fitzpatrick on the case. On the question of drainage, he felt that all lung hydatid cysts should be drained, but with those of the liver this was not necessary. He inquired whether the hooklets of the hydatids were able to reproduce more cysts or whether it was necessary to have daughter cysts for that to take place.

DR. H. I. HOLMES congratulated Dr. Fitzpatrick on his extrusion methods for removal of lung hydatid cysts. With regard to hydatid of the liver he thought that closure was necessary. When there was calcification present closure should be effected whenever possible, otherwise infection would take place. Nothing appeared to dissolve calcification. On the question of eosinophilia, he considered that serial estimates were sometimes of value in deciding the question whether further hydatid cysts were still present.

PROFESSOR E. S. J. KING said that he wished to stress one point in pathology. As the hydatid cyst enlarged the enlargement was usually towards the periphery of the lung, but it would come in contact with some bronchus. There was therefore a potential connexion between the hydatid and the bronchus, and that explained why rupture occurred. He felt that that was the reason why drainage of lung hydatid cysts was necessary to prevent the risk of a sudden "blow up" in the chest.

Dr. Fitzpatrick thanked the speakers for their congratulations. He said that he had found that cases of hydatids were increasing in his area, and he felt that the fact that dogs were still being fed on offal containing cysts was a large factor. He mentioned that brood capsules and scolices fell to the bottom of a cyst, and if the surgeon was careful there was no need to spill them during operation. With regard to the question of drainage, if there was a slight rise in intrapulmonary tension there was often a break through from the cavity of the hydatids into the bronchus. It was therefore necessary to provide for the escape of gas.

Lymphatic Leuchæmia.

DR. W. G. MILLER presented a girl, aged three years, who had had a history of tonsillitis for three weeks before admission to hospital; it had been treated with sulphadiazine. She was admitted to hospital as a very pale, listless little girl, with normal temperature, and apart from a presystolic triple rhythm, no abnormality was found on examination. She was regarded as having aplastic anæmia for investigation. However, for the next month the blood picture and finally a sternal marrow biopsy showed the condition to be one of lymphatic leuchæmia. A course of ACTH and aureomycin was given without any noticeable effect. Transfusions had been administered and still appeared necessary.

DR. ROBERT SOUTHBY pointed out that the history of sore throat or tonsillitis before the first symptoms of leuchæmia was met with quite often. The varying blood picture in the present case was of interest. He had seen a number of children present in the same way, the condition starting as infection, passing to aplastic anæmia and then finally showing itself as leuchæmia. Also of interest was the therapy. Aureomycin *et cetera* were of not much help except to prolong the illness. Dr. Southby raised the question whether repeated blood transfusions should be carried out in such cases. The Red Cross Blood Transfusion Service was vitally concerned in the matter, and at the Children's Hospital in Melbourne it was explained to the parents of such children that relatives, if possible, should become blood donors. With regard to ACTH and aureomycin, he felt that members of the profession should take a firm stand; therapy such as that should not be used unless it was of proven use, and members should not be swayed by articles in the daily Press.

Splenic Enlargement: Reticulosis.

Dr. Miller's second patient was a married woman, aged thirty-seven years, who first had presented with pain on defæcation due to *fissure in ano*. She had also complained of pain in the right groin. X-ray examination showed a large, firm, oval, smooth mass in the left upper part of the abdomen extending down almost to the umbilicus. Blood examination, Casoni tests and other investigations were carried out. It was decided to perform laparotomy, and this revealed a smooth, uniformly enlarged, congested spleen. The liver was normal. No enlargement of the portal system was found. The spleen was not removed, and a diagnosis of splenic anæmia was considered most likely. A year later the patient presented complaining of increasing discomfort from the enlarged spleen. It was decided to review the case fully, and at that time the following sternal marrow findings were reported:

> The marrow appears normoplastic or slightly hypoplastic, but there may be some slight dilution by admixture of blood. This admixture would, however, hardly affect the myeloid cell/nucleated red cell (M/E) ratio which, although still within normal range, is slightly lower than in previous marrow film examined. There is also a definite shift to the left in the myeloid series as compared with previous film. These two features together suggest some degree of maturation arrest of the myeloid white cell series. These findings are partly consistent with those found in splenic anæmia (which one would expect to have developed to some degree by this time in this patient) and also some maturation arrest in megakaryocytic tissues, leading to thrombopenia, which was not evident. Hypersplenism, restricted in its activity to the myeloid leucocytic system, must also therefore be considered.

After further discussion, operation with a difficult splenectomy was performed, the liver still being normal in size and appearance. Convalescence was uneventful, but a few months later small palpable glands were present in both axillæ. However, a pathological report on a biopsy from the spleen and a lymph node strongly suggested that the condition was one of the reticuloses and conformed with that of giant lymphoma.

DR. A. C. NEWELL asked why neutropenia was present if the case was one of hypersplenism.

PROFESSOR E. S. J. KING pointed out that all cases of reticulosis were a difficult problem. As far as histological examination was concerned, a definite diagnosis could often be given, but not always. There were other means of diagnosis as well, but even then a heterogeneous group was left, the members of which were not well understood. Typical in the present case was a giant lymphoma identified histologically, and it was known that that condition was progressive and uncontrollable by treatment. The effect on the bone marrow in such a case could be most variable.

Dr. Miller, in reply, said that he thought that the relatively normal bone marrow in the case under discussion was rather

amazing. He said that the physiology of the bone marrow was still little understood. The spleen must have some effect on the leucopenia because of the leucocytosis occurring post-operatively.

Hydatid Cyst of the Liver.

DR. W. R. ANGUS presented two patients, the first, a man, aged fifty-six years, who had presented complaining of pain in the chest on breathing and pain in the neck. He had been in good health before this occurred, and he gave a history that a few days previously he had lifted some heavy timber and strained his shoulder. X-ray examination showed a dense opacity at the base of the left lung consistent with an effusion. The left side of the diaphragm was elevated, and a large rounded mass with peripheral calcification was present below it. This was considered to be a calcified hydatid cyst of the left lobe of the liver. The results of a Casoni test and a complement-fixation test were strongly positive. Dr. Angus went on to describe the surgical approach that had been made by a subpleural trans-diaphragmatic route. The method had been suggested and adopted after consultation with Dr. Fitzpatrick, and it had been found most suitable. The cyst was freely opened and the contents were evacuated. Post-operative convalescence was uneventful, but the patient still had sinus discharge at intervals.

Dr. Angus pointed out during the discussion that he considered that two factors had lessened the risk of hydatid disease—one was the increasing use of motor-cars and the lessened risk of close contact with sheep dogs, and the second was the use of vermifuge powders for dogs.

Sjögren's Syndrome.

Dr. Angus's second patient was a woman, aged fifty-four years, who was considered to be suffering from Sjögren's syndrome. She complained of blurring vision and itching of her eyes, the left eye being the worse; neither eye ever watered, but a thick discharge occurred across the eyes. Onions caused stinging to the eyes, but produced no discharge. The mouth did not water when the patient sucked a lemon. Five years before, she had begun to develop arthritis of the feet and hands, and later of the back.

Dr. Angus demonstrated the patient's condition and also the use of the Schirmer test in such a case, using filter paper placed under the lid of the eye; he also demonstrated the use of the rose bengal test and pointed out that both of these tests were simple and both demonstrated diminished lachrymal secretion. Dr. Angus said that he thought that both *keratoconjunctivitis sicca* and rheumatoid arthritis might be manifestations of a generalized collagen disease throughout the body. He showed that the pathology of Sjögren's syndrome was essentially chronic œdema followed by hydropic degeneration and atrophy of the epithelium as the result of a primary lesion in the lachrymal glands. He explained that mucin still helped to keep the eye lubricated. Finally he discussed the management of such a case in the light of present knowledge.

Radiological Aspects of Gastric Neoplasms.

DR. A. T. PARK discussed the radiological aspects of various malignant and benign gastric neoplasms with special reference to the patients who had been presented during the meeting.

The Pathology of Common Chest Conditions.

PROFESSOR E. S. J. KING gave a lecture, profusely interspersed with lantern slides, on the subject of the pathology of common chest conditions.

DR. ROBERT SOUTHBY pointed to the change in the type of pneumonia now met with. He wondered whether this was the result of chemotherapy or due to a change in the organisms present. He felt that the bacteriological report on the type of organism was of help in treatment. He wondered why, with subacute nephritis, the serous membranes were particularly liable to be picked out.

Professor King said, in reply, that he felt that the change in pneumonia might possibly be due to chemotherapy. With regard to serous membranes in subacute nephritis, those were affected by the disease and were therefore more liable to be infected.

DR. W. G. MILLER thanked Professor King for his lecture and asked whether he would explain how to pick ante-mortem from post-mortem clot in the heart. He also asked what was the mechanism of death in pulmonary infarction.

Professor King said that the differentiation between ante-mortem and post-mortem clot was not easy and needed experience. If the clot was adherent and laminated, then it was ante-mortem clot. With regard to the second question, he wondered whether a reflex coronary spasm might not be the cause of death.

DR. H. C. MALING said that, in his experience, when post-mortem examinations were made in cases of sudden death all that was found sometimes was atheroma. He wondered if it was reasonable to attribute death to that cause.

Professor King pointed out that in coronary infarction and sudden death only 12% of cases showed a definite lesion. He said that change in the cardiac muscle would not be found unless the coronary accident had occurred twelve to eighteen hours previously. There might be a loss of the blood supply to the heart not due to any actual lesion but more the result of thickened coronary vessels. He felt that the problem was often of medico-legal importance.

DR. C. B. BERRYMAN asked Professor King what was the real pathology of coronary arterial disease.

In reply, Professor King pointed out that the idea of hæmorrhage into an atheromatous plaque was untenable.

DR. K. HALLAM said that he noted that Professor King had mentioned that although extensive tuberculosis might be present in the chest *post mortem*, that might not be the cause of death. He mentioned that at the Royal Melbourne Hospital, 30% of the post-mortem examinations showed active tuberculosis when the cause of death had been something else. Nowadays, X-ray examination of the chest was a very common procedure, and he felt that it was important that the fact that a tuberculous lesion was found at X-ray examination should not stop the clinician from making full and complete efforts to arrive at the full diagnosis.

DR. H. I. HOLMES asked Professor King whether recent pathology had revealed any relationship between tuberculosis of the lung and pulmonary malignant disease.

Professor King pointed out that this was an old idea, originally developed by the late Professor Cherry. It was now considered that there was no real relationship.

Finally, Dr. Maling proposed, and Dr. Southby seconded, a vote of thanks to Professor King.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

GAOL AND CIVIL HOSPITALS.[1]

Colonial Secretary's Office,
17 January, 1827.

James Bowman, Esq.,
PRINCIPAL SURGEON.

Sir,

The proceedings of a Board appointed to enquire into the Conduct and management of the Gaol and Civil Hospitals and the treatment of the sick on board the HULIS having been submitted to the Governor I am directed by His Excellency to Communicate to you the following particulars.

In the gaol it appears that the Assistant Surgeon has not had sufficient power for the removal of a patient to the Civil Hospital even in serious cases, without the permission of the Sheriff whereby in two particular instances a delay of some importance has been caused. To remedy this an arrangement will be made with the Sheriff by which the Medical Officer will be empowered to remove a Patient (if confined at the instance of the Crown) whenever requisite without waiting for further authority, on furnishing the Governor of the Gaol with a written certificate of the necessity of his doing so. This power being given to him he will be held strictly responsible that every removal be made in one time, and, still further to guard against negligence in this respect, he will be required to submit a daily nominal report of the sick of that establishment with a specific remark against the name of each who requires to be sent to the Civil Hospital.

His Excellency remarks however a great irregularity which has existed since 29th April 1820 in omitting to note

[1] From the original in the Mitchell Library, Sydney.

the prescriptions and progress of diseases as was done up to that date. He desires accordingly that you will communicate this observation to Mr. Assistant Surgeon McINTYRE and enjoin him to keep for the future a Book in which the detailed symptoms and History of every case shall be regularly entered, with the treatment practised and the appearances on dissection of those that die—which book is to be kept in the dispensary of the place and ready for inspection whenever required. On board the Hulk the Board recommend that a Hospital be fitted up for the reception of twenty men, and His Excellency so far concurs in the eligibility of the claim that He has instructed the Civil Engineer and Master attendant to report on its practicability, but he is of opinion that the scale proposed is too extensive, as a removal to the Civil Hospital must always be expedient in dangerous cases, and as the Sheriff does not interfere in this Establishment the difficulty experienced in the Gaol cannot be felt.

The same irregularity however is apparent in the want of proper books, calling for the same remarks, and to be remedied by giving the same instructions respecting a daily nominal report, and detailed register of the progress and treatment of diseases as already prescribed for the Gaol. Strict responsibility for non-removal when required, of course, attaches equally.

In the Civil Hospital His Excellency has the satisfaction to learn that although no warning was given the Board found the wards perfectly clean, and everything well arranged with the exception of a portion of the Bedding which appeared old and worn out, and for inspecting which and replacing such part of it as may be unserviceable, arrangements will shortly be made.

In the meanwhile on the representations of the Board that it would add much to the convenience, directions have been given to complete with doors, locks, and windows, the outbuildings intended respectively for Your Office and for places of solitary confinement. With the view also of ensuring the due performance of the prescribed duties in Sydney and the regular and proper distribution of medicines to all the hospitals and outposts throughout the Colony, His Excellency is pleased to sanction the appointment of an additional assistant surgeon and of an apothecary. For the first of these situations Mr. William Elyard formerly Surgeon of HM Ship Josephine having offered himself as a candidate, His Excellency directs that you will take an early opportunity of reporting on his fitness, for which purpose the gentleman has been requested to wait on you. For the other situation, that of apothecary You will be pleased to recommend a fit person as soon as practicable, with the understanding however that the appointment will be but temporary as it will be filled ere long from home.

In the course of this examination the Board found reason to form the opinion that the system generally adopted, in the medical Establishments throughout the Colony, would be much improved by adding the following Books and Returns to those already kept, as they would elucidate in a clear manner every point on which information might hereafter be required—viz.:

A Half Yearly return of Hospital Bedding and Stores.

A Register for cases of Vaccination and Small Pox.

A monthly nominal Return of the sick at each Station.

A quarterly nominal Return of the same (already ordered).

A medical Register as above directed for the Gad and Hulk for the insertion of the detailed history of every case of disease, together with the treatment practised, and the appearances on dissection of those who die.

His Excellency accordingly commands, that you will give directions for these several Books and Returns to be kept and furnished at each of the Establishments under your control throughout the colony, agreeably to the military Forms which you will be pleased to obtain and forward for that purpose.

I have, &c.,
ALEXR. McLEAY.

Correspondence.

GENERAL PRACTITIONER GROUPS.

SIR: Dr. Winterbotham's letter (THE MEDICAL JOURNAL OF AUSTRALIA, July 5, 1952) warrants some comment. He quotes "in time of peace prepare for war". Another quotation more applicable to the present time is "whatsoever a man soweth, that he shall also reap".

"Not only in country hospitals", but elsewhere by reason of the free hospital scheme of Queensland socialistic government, medical men are feeling the "pinch". The scheme of free hospital treatment was introduced in the later years of the war, and the failure of the profession to oppose it is tending to deprive many practitioners of what should be rightly looked upon as their birthright.

I hope Dr. Winterbotham's attempt to awaken the profession is not too late.

Yours, etc.,
July 5, 1952. "S.P."

PUBLIC HEALTH ASPECTS OF WATER FLUORIDATION.

SIR: The article on public health aspects of water fluoridation by H. Hilleboe and D. Ast (*American Journal of Public Health and The Nation's Health*, November, 1951), abstracted in THE MEDICAL JOURNAL OF AUSTRALIA, June 21, 1952, completely ignores the very important work of Weaver, an excellent account of which is published in *Proceedings of the Royal Society of Medicine*, Volume XLI, page 284 (May, 1948).

The statement that a fluorine level of one part per million, occurring naturally in a communal water supply, will reduce the incidence of dental caries in children by 60% to 65% is being copied, with complete absence of critical analysis, by one writer after another, in popular and pseudo-scientific journals. As far as it can be said to have any basis whatever in any scientific observation, it appears to be founded upon Weaver's investigation of the children in North Shields and South Shields. In this, it was discovered that the children in the town which had a water supply containing 1·4 parts per million of fluoride had appreciably less dental caries than children of the same age group in the other town. For example, the twelve-year-old group in South Shields had only 56% of the average "D.M.F." rate (permanent teeth) of the same age group in North Shields. But when the investigation was carried further, it was discovered that the average "D.M.F." rate in fifteen-year-old children in South Shields was the same as that of the twelve-year-old group in North Shields.

The only conclusion that one can justifiably draw from these figures is that the effect of naturally occurring fluoride in a town water supply was to postpone the average stage of progress of dental caries by approximately three years. The statement of certain American authors, that "by forthright action, the public health officer can move forward in effectively implementing this programme, so that our next generation of children may approach adulthood with a full complement of teeth" suggests uncritical enthusiasm rather than scientific inquiry. It may be true; but, if there is any evidence, available at the present time, from which such a conclusion can be justifiably reached, many thousands of people concerned with child health throughout the world would be glad to hear of it.

Yours, etc.,
H. M. L. MURRAY,
Director of Public Health.

Hobart,
July 1, 1952.

URINARY CALCULUS: SOME NOTES ON ITS HISTORY AND MODE OF FORMATION.

SIR: In medical history, as in all other departments of knowledge, erroneous assumptions are copied from text-book to text-book, until they become erected as general principles which cannot be shaken by the facts which contradict them. Thus it has been said a thousand times that medical knowledge nearly died out in Europe during the years A.D. 500 to 1200, and that it was kept alive only in Arabia and Persia. Professor King (THE MEDICAL JOURNAL OF AUSTRALIA, June 21, 1952, page 837) falls into this error, with an addendum that Christian persecutions drove eastwards the only possessors of medical knowledge.

Of course it is not true. There is plenty of evidence that medical knowledge was handed on in Europe as a direct tradition. A. Castiglioni ("A History of Medicine", 1941) devotes 11 pages to the medical documents which have survived to show that the Hippocratic tradition was kept alive when civilization was at its lowest ebb.

In the sixth century, in the Ostrogothic kingdom of Italy, Cassiodorus wrote his famous letter to the supervising physician of the royal household, in which he restates many of the principles of Hippocrates and refers to the standards of medical practice set up for a profession regulated by the

Government. A century before this a medical code was laid down by the Visigothic king in Spain.

L. C. MacKinney (*Bulletin of the History of Medicine*, January, 1952) has given detailed study to 16 Latin manuscripts, now in various libraries of Europe, which have survived from periods as early as the eighth century and no later than the twelfth. They deal mostly with medical ethics and etiquette, with a good deal about the qualifications and training of the physician. They show the influence of Hippocrates in almost every line, but there is less of Galen in them.

J. D. Comrie ("History of Scottish Medicine", 1932) has shown that medical knowledge was kept alive in Northumbria and Scotland. Bede (seventh century) in his "Life of St. Cuthbert" gives evidence of wide medical knowledge. "The Leech Book of Bald", a Saxon medical manuscript dating from 900, shows the influence of a Latin education and contains many quotations from Byzantine writers, such as Paulus of Ægina, who wrote in the seventh century. Travel to Palestine was not uncommon, and the author mentions remedies which had been sent from Jerusalem. The book was written for Bald, a physician, by a monastic scribe named Cild; there was a special class of lay physicians or leeches, and medicine was by no means confined to the clergy. Many of the lay healers were addicted to the use of amulets, and Bede tells us that Cuthbert and other monastic teachers were continually preaching against these superstitious practices. Comrie mentions also two twelfth century manuscripts which were used in Scotland and are now in the National Library at Edinburgh. One is a commentary in Latin on Galen and Hippocrates, by Johannicus, a pupil of John of Alexandria.

The decline of civilization in the Dark Ages was due to incursions of barbarians who burned and looted; innumerable valuable manuscripts perished at their hands. Knowledge (including medicine) was kept alive in the monasteries where hospitals were built for the sick; but medical practice was not restricted to the clergy. In Rome the present Hospital of the Holy Spirit was founded in the twelfth century, on the site of the *Schola Saxorum*—a hostel erected by a Saxon king in the seventh century for the benefit of sick Saxon pilgrims in Rome. In the Middle East and North Africa the Moslems pillaged and burned, and destroyed a whole civilization. In the British Isles the damage done by the Danes was colossal. It is little wonder, therefore, that only a few medical manuscripts have survived. But those which do exist prove beyond doubt that the Hippocratic tradition never died out in Europe.

Yours, etc.,

34 Queen's Road,
Melbourne,
July 1, 1952.

MICHAEL KELLY.

CHEMOTHERAPEUTIC ADVANCES IN TROPICAL DISEASES OF IMPORTANCE TO AUSTRALIA.

SIR: The issue of THE MEDICAL JOURNAL OF AUSTRALIA of May 10, 1952, arrived here only a few days ago. I therefore apologize for writing this letter with so much delay.

I have read with great interest Sir Neil Hamilton Fairley's paper "Chemotherapeutic Advances in Tropical Diseases of Importance to Australia", particularly his views on the treatment of typhoid and paratyphoid fevers.

During the last three years the incidence of typhoid and paratyphoid in Calcutta has been so great that I can now look back on well over two hundred cases in private practice treated with chloramphenicol without a single fatality. With a few exceptions these cases have come under my treatment within the first or second day of their disease, and treatment could be started almost immediately, after the Widal reaction was found suggestive. In about 70% of the cases blood culture was positive. In more than 50% the disease started abruptly, usually during the night, with shivering and fairly high rise of temperature, which appears to be the type of typhoid or paratyphoid prevalent here.

It has been my practice to start treatment with a loading dose of 3·0 grammes, and to continue with 3·0 grammes per day until fever subsided, and then to continue with 1·5 grammes per day for five days only. Under this regime there has not been one single relapse amongst those cases in whom treatment was started within the first three days of the disease. Altogether my relapse rate has been below 2%. Three cases have relapsed, two paratyphoids and one typhoid, and in those three cases treatment was not started within the first three days.

This observation of complete absence of relapses in those cases treated early is at variance with the theoretical considerations of Sir Neil's, that a relapse is less likely to occur when the body has been able to build up immunity. But does the body build up any immunity against typhoid at all? With growing practical experience this appears to me more and more doubtful. Typhoid is, after all, the disease *par excellence* which relapses even after the body ought to have built up some immunity throughout a long course of feverish illness. How different is this tendency to relapse from the course run by diseases which produce real immunity like smallpox or measles!

Amongst my observations has been one European who was ill for nearly three weeks when I saw him first. He had been mistakenly treated for malaria, but his typhoid had not been very severe and he was free of fever within a few days after chloramphenicol treatment. This same patient reported ill five months later, and the diagnosis was again typhoid, blood-culture positive. It was then proved that his servant was a carrier. Where was his immunity after having run through the whole course of typhoid only five months before?

There has been a large number of cases in this series who had had their full course of inoculations from a few weeks to a few months before they fell ill. It did not seem to make any difference whether the vaccine had been prepared and injected here or abroad, protection was not achieved. I am well aware of the fact that these observations differ greatly from the experiences made by the armies during the late war and in Korea. It proves, however, that typhoid immunization is only relative and is broken through easily if the infection is massive enough, as is probably the case in Calcutta, where carriers are obviously much more numerous than amongst army personnel.

Yours, etc.,

43 Chowringhee Road,
Calcutta 16,
India.
June 30, 1952.

RUDOLF TREU.

THE DANGERS OF ANTIBIOTICS.

SIR: Dr. E. Thomson's timely article, "The Dangers of Antibiotics", in your issue of June 28 confirms the need for apprehension concerning the unscientific use of antibiotics.

In stating, however, that the *Neisseria gonorrhœæ* still remains antibiotic sensitive, the author is possibly confining his remarks to the strains he has encountered in his own laboratory. As long ago as 1949, and three years is a long time in the history of antibiotics, cases of penicillin-resistant gonorrhœa were frequently cropping up in England among seamen. These strains were apparently acquired in Italian and South American ports. They arose presumably from the misuse of penicillin in the same way that sulphonamide-resistant strains had arisen previously. It can only be a matter of time before penicillin resistant gonorrhœa appears in Australia if, indeed, it is not yet here.

Dr. Thomson's table purporting to show the increasing penicillin resistance of *Staphylococcus pyogenes* is not convincing. He has lumped together data collected in various parts of England and Australia relating to in-patients, out-patients and "hospital patients". Does the last group represent a random assortment of the first two?

One suspects, also, that the table relates to varying degrees of insensitivity unless in each case an identical technique was used and the concentration of antibiotic did not vary, a consummate exercise for statistical purposes, but, in fact, too good to be true.

Furthermore, even as they stand, the figures do not prove that "there has been a steady increase in the incidence of penicillin-resistant . . . strains in various parts of the world". Thus, hospital patients (Barker, London) produced 59% resistant strains in 1948 and 35% in 1949, and the latter figure is 3% lower than the 1947 figure. The only data for 1950 relate to out-patients in Sydney, but it is of little value unless we know the corresponding out-patient figure for the same hospital for the previous year.

A comparison of strains isolated by Dr. Thomson and others in the periods October, 1948-March, 1949, and April, 1949-March, 1950 shows a decline in penicillin-resistant strains from 53% to 49% in the second period.

While clinical experience suggests we are undoubtedly meeting more and more penicillin-insensitive strains of *Staphylococcus pyogenes*, the figures quoted can hardly be offered as experimental evidence to prove the point.

Yours, etc.,

Hadley Street,
Pittsworth,
Queensland.
July 1, 1952.

COLIN KENDALL.

University Intelligence.

UNIVERSITY OF MELBOURNE.

THE eighteenth Halford Oration will be delivered by Professor E. C. Dodds in the Public Lecture Theatre of the University of Melbourne on August 21, 1952, at 8.15 p.m. The subject will be "Some Biochemical Aspects of the Problem of Aging". All members of the medical profession are welcome.

Post-Graduate Work.

SEMINARS AT THE ROYAL PRINCE ALFRED HOSPITAL, SYDNEY.

THE honorary secretary of the Seminar Group, Royal Prince Alfred Hospital, Sydney, announces that seminars open to all members of the medical profession will be held in the A2 Lecture Theatre on Fridays from 1.15 p.m. to 2.15 p.m. during the period July 18 to October 31, 1952. The programme will be as follows:

July 18: Cardiology section, "Anticoagulant Therapy, Part II". July 25: Hæmatology section, "Modern Trends in the Treatment of Leuchæmia and Allied Conditions". August 1: Endocrinology and metabolism section, "Gout". August 8: Gastro-enterology section, "Ulceration within the Mouth". August 15: Thoracic section, "Antibiotics and Drug Therapy in Pulmonary Disease". August 22: Neurology section, "Intracranial Vascular Anomalies". August 29: No seminar. September 5: Pædiatrics section, "Acute Poisonings in Childhood". September 12: Cardiology section, "Heart Disease in Pregnancy". September 19: Pathology section, clinico-pathological conference. September 26: Hæmatology section, "The Role of the Bone Marrow in Hæmatological Diagnosis". October 3: Thoracic section, "Hæmorrhagic Pleural Effusions". October 10: Gastro-enterology section, Dr. Avery-Jones (London), subject to be announced later. October 17 and 24: No seminar (Royal Prince Alfred Hospital Medical Officers' Association reunion fortnight). October 31: Endocrinology and metabolism section, talk by Dr. T. M. Greenaway on impressions abroad.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointment has been promulgated in the *Commonwealth of Australia Gazette*, Number 43, of June 19, 1952.

AUSTRALIAN MILITARY FORCES.

Australian Regular Army.

Royal Australian Army Medical Corps: Medical.

To be Captain, 10th April, 1952, with a Short Service Commission for a period of one year.—3/40099 John Martin Bradley (Captain).

Australian Medical Board Proceedings.

QUEENSLAND.

THE following have been registered, pursuant to the provisions of *The Medical Acts*, 1939-1948, as duly qualified medical practitioners: Bainbridge, Fred, M.B., B.S., 1951 (Univ. Melbourne); Wood, Alan John, M.B., B.S., 1951 (Univ. Melbourne); Batt, Betty Joan, M.R.C.S. (England), 1948, L.R.C.P. (London), 1948, M.B., B.Chir., 1948 (Univ. Cambridge); Batt, Eric Harrison, M.B., Ch.B., 1946 (Univ. Leeds); Morrissey, John James, M.B., B.S., 1951 (Univ. Melbourne); Prentice, David Hugh, M.B., B.S., 1947 (Univ. Sydney).

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JUNE 21, 1952.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	..	..	..	1	..	..	..	1
Amœbiasis	..	..	1	..	..	..	..	..	1
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	1(1)	..	1(1)	..	..	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	..	..	3(2)	..	3(3)	..	1	..	7
Diphtheria	10(4)	8(7)	9(4)	..	2(1)	..	..	..	29
Dysentery (Bacillary)	..	2(2)	6(6)	..	..	..	..	2	10
Encephalitis	..	..	..	2(1)	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	..	..	..	..	15(5)	..	..	..	15
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	3	..	..	..	3
Leptospirosis	..	..	1	..	..	..	..	..	1
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	3(2)	7(4)	2(1)	2(1)	..	..	..	..	14
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	5(1)	3	1	3(3)	1	..	..	..	13
Puerperal Fever	..	..	1	..	..	..	..	..	1
Rubella	..	5(4)	..	..	1(1)	..	..	..	6
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	26(9)	28(16)	14(13)	3(2)	4(3)	5(2)	..	..	80
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	32(23)	18(16)	16(10)	12(12)	16(10)	5(2)	1	1	101
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	2	..	2(2)	..	..	..	4
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

TASMANIA.

THE following have been registered, pursuant to the provisions of the *Medical Act*, 1918, as duly qualified medical practitioners: Lane, Harold Arthur, M.B., B.S., 1945 (Univ. London), M.R.C.S. (England), 1945, L.R.C.P. (London), 1945; Buley, Lloyd Edgar, M.B., B.S., 1951 (Univ. Melbourne); Quinlan, John Thaddeus, M.B., B.Ch., 1928 (Nat. Univ. Ireland).

Notice.

VICTORIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION.

Proposed Section of Industrial Medicine.

THE Council of the Victorian Branch of the British Medical Association has given approval to the proposal that a Section of Industrial Medicine be established within the Branch. All members of the Branch interested in proceeding with the matter are invited to attend a meeting at the Medical Society Hall, 426 Albert Street, East Melbourne, at 8.15 p.m. on Wednesday, July 30, 1952.

Obituary.

COLIN GRAY.

WE regret to announce the death of Dr. Colin Gray, which occurred on May 12, 1952, at Maldon, Victoria.

JOSEPH RUSKIN CORNISH.

WE regret to announce the death of Dr. Joseph Ruskin Cornish, which occurred on July 4, 1952, at Adelaide.

Medical Appointments.

The following appointments have been made, pursuant to the provisions of Section 18 (2) of the *Mental Hygiene Authority Act*, 1950, of Victoria: Dr. G. A. Wright and Dr. J. K. Adey to be senior medical superintendents; Dr. T. G. C. Retallick, Dr. E. L. Roberts, Dr. G. A. Golding, Dr. H. C. Stone, Dr. H. J. C. Edmonds and Dr. J. F. J. Cade to be medical superintendents; Dr. G. C. Jago to be a pathologist; Dr. V. P. Johnson, Dr. A. R. Phillips, Dr. R. E. G. MacLean and Dr. J. V. Ashburner to be psychiatrists; Dr. J. L. Gorman, Dr. D. R. Moore and Dr. Marjorie Gilchrist to be assistant psychiatrists; Dr. S. J. Cantor, Dr. W. A. J. Brady, Dr. S. P. Derham, Dr. R. R. Webb, Dr. L. L. Lovett, Dr. N. Morrissy and Dr. Margaret Heggie Troup to be senior medical officers; Dr. K. J. Meagher, Dr. V. L. Matchett, Dr. H. M. Bower, Dr. N. A. Maclure, Dr. C. H. Noack and Dr. J. L. Fordyce to be medical officers.

The following appointments have been made, pursuant to the provisions of the *Mental Hygiene Act*, 1928, as amended by the *Mental Hygiene Authority Act*, 1950, of Victoria: Sir Harold Gengoult Smith and Dr. P. Gilbert to be official visitors to the Mental Hospital and Receiving House, Royal Park; Dr. I. H. K. Matthews to be an official visitor to the Mental Hospital, Ararat.

Nominations and Elections.

THE undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Walker, Ronald Jeffrey, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951), 70 Harrow Road, St. Peters, South Australia.

O'Connor, John Desmond, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951), 38 Opey Avenue, Unley, South Australia.

Hughes, John Burnell, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951), 41 Marlborough Street, Brighton, South Australia.

Tarlton-Rayment, James, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951), Barmera, South Australia.

Barnes, Robert, M.B., B.S., 1948 (Univ. Adelaide), 3 Kerta Weeta Avenue, Black Forest, South Australia.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Drever, Ian Campbell, M.B., B.S., 1951 (Univ. Adelaide) (qualified December, 1950); Shea, Brian Joseph, M.B., B.S., 1951 (Univ. Adelaide) (qualified December, 1950); Davenport, John, M.B., B.S., 1952 (Univ. Adelaide) (qualified December, 1951).

Diary for the Month.

JULY 22.—New South Wales Branch, B.M.A.: Ethics Committee. Council Meeting.
JULY 23.—Victorian Branch, B.M.A.: Council Meeting.
JULY 24.—New South Wales Branch, B.M.A.: Clinical Meeting.
JULY 25.—Queensland Branch, B.M.A.: Council Meeting.
JULY 31.—New South Wales Branch, B.M.A.: Branch Meeting.
JULY 31.—South Australian Branch, B.M.A.: Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital: all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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